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# THE JOURNAL OF PEDIATRICS

A MONTHLY JOURNAL DEVOTED TO THE PROBLEMS AND DISEASES OF INFANCY AND CHILDHOOD

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# The Journal of Pediatrics

VOL. 36 JUNE, 1950 No. 6


## Original Communications

### THE PEDIATRICIAN'S RESPONSIBILITY IN THE PREVENTION OF DENTAL CARIES


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CHICAGO, ILL.


THE HEALTH of a child today is dependent upon a very complex routine of immunizations, dietary supplements, and vitamin concentrates managed by parents and physicians. Children today are by far more healthy than were children 100 years ago and interest in children as future citizens, who should be able to grow and develop to adulthood without retardation or impairment, has reached a new peak. Parents are better educated regarding their children and physicians are better equipped to meet the medical problems that arise. Yet, dental desease of children seems to go on unchecked, seemingly involving more children and younger children today than a century ago. Estimates have been made that 98 per cent of all school children in the elementary grades have suffered the effects of this disease in varying degrees of severity. It is so common that frequently a desperate situation must arise that involves pain or an acute infection before some get concerned over it.

Many reasons might be given to account for this; however, six reasons of importance might be listed as follows:

1. Lack of parental knowledge and understanding of the importance of early dental care.
2. Lack of interest on the part of the dentist in the care of children, or the fear of a dentist of an unmanageable child.
3. Fear on the part of the child of the dentist as developed by adult conversations, cartoons, and jokes.
4. Lack of interest until recently on the part of the clinical dental practitioner in the study of children's problems and how to cope with them.
5. Lack of personnel in the dental profession.
6. Incomplete knowledge of the nature of dental disease.

These reasons might be similar to the ones that existed in the early days of medical practice before the development of the specialty of pediatrics to the high standards it represents today.

Today, children are regarded as patients requiring exacting dental care. As clinical knowledge has increased and as dental research has progressed, more and more emphasis is being laid by dental educators upon the need for early


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dental care of the most complete kind. Emphasis on the preventive side of dental caries has taken great strides forward in the last few years and now a definite program can be given to parents that should greatly reduce the individual child's problem. The pediatrician, as the chief consultant for the parents of his patients, is in an excellent position to start the young child down the right road. With this in mind, the pediatrician should be fully acquainted with dental caries as it affects children, and with the most recent information regarding the prevention of this disease.

The understanding of the etiology and pathology of dental disease as it affects the child's mouth is dependent upon the anatomy and physiology of that area. Therefore, a brief review of the structures under consideration is in order, so that there is no confusion about terminology.

All teeth, deciduous and permanent, are made up of enamel, dentin, and cementum, and contain blood vessels and nerves within the pulp chamber. Each tooth is separately attached to the underlying bony structure by means of a fibrous ligament called the peridental membrane. The teeth are surrounded in the mouth by a mucous membrane which is attached to the necks of the teeth and is called the gingivae. The deciduous teeth serve as functional units in the child's mouth until the permanent teeth are formed and the facial bones develop to the point that they can accommodate these larger teeth. Deciduous teeth are similar to permanent teeth in every way with the exception of size and morphology.

In most instances, the maintenance of the deciduous teeth to full term is essential to the proper eruption and positioning of the succedaneous permanent teeth. Physiologic resorption of the roots of the deciduous tooth begins when the permanent tooth replacing it begins to erupt; and eventually, the deciduous tooth is shed as a result of complete loss of root structure. Nature has provided an eruption pattern for the permanent teeth so that a normally developing mouth always has two types of teeth, one for incising and one for grinding. To accomplish this the first permanent tooth erupts, when the child is approximately 6 years of age, behind the last deciduous tooth in each quadrant of the mouth. Then, the next permanent teeth to erupt are the incisors in the anterior part of the mouth. Within the next five or six years the intervening teeth erupt, followed within the next two to five years by the remaining back teeth. Each of these erupting teeth is dependent on its neighboring teeth for its position, together with the muscular pressures of the lips, cheeks, and tongue. Thus there is a definite pattern to the development of the normal adult mouth, and there are many factors involved in developing such a relationship of the teeth. It is therefore logical to find that any loss of dental units, or disturbance in this pattern of eruption and development, may result in malposition of the permanent teeth, thus crippling complete function of the mouth. A malocclusion developed in this way can become a serious problem in adult years.

With this brief review of the facts expressing the importance of childhood years in the development of a normal mouth, its anatomy and physiology, it next becomes our problem to know what dental disease is most prevalent in children and how it may be managed.

Dental caries is the most widespread and most common dental disease of the people in this country, especially of children. Dental caries seems to affect children's teeth more rapidly and with more damaging results. This occurs inasmuch as the deciduous teeth are smaller, therefore more vulnerable to attack. Also the young permanent teeth being incompletely developed, have larger pulp chambers and dentin of more permeable nature. For these reasons, together with the irregularity of children's habits, the problem of dental caries is the major problem in maintaining oral health for children. Methods of control and prevention are essential to the successful management of the child patient.

Dental caries has been considered a mystery, unsolved except by theory, for years. Various schools of thought developed in various parts of the country. Each group felt that it was in disagreement with the others, whereas, in reality, they were quite close to the same idea. This was demonstrated in September, 1947, at the University of Michigan. At that time, more than one hundred dentists, physicians, biochemists, nutritionists, and dental health educators enrolled at Ann Arbor to attend a workshop on the evaluation of the caries problem, its prevention and control. One of the most important results of this meeting was the work of the committee that prepared and presented a definition and explanation of the process of dental caries as it is known today. This definition, which was prepared by analysis and study of the numerous accepted research studies that have been recorded in the literature and was based on a theory that was first advanced before 1900, has stood the test of time and has been greatly elaborated upon. The accuracy of this definition was emphasized by its unanimous acceptance by the entire group representing many different schools and research teams from over the country. Upon this definition the whole of caries prevention and control and its complexity can be understood. Therefore, part of it is quoted as follows:

"Dental caries is a disease of the calcified tissue of the teeth. It is caused by acids resulting from the action of microorganisms on carbohydrate and characterized by a decalcification of the inorganic portion, and accompanied by, or followed by, a disintegration of the organic substance of the tooth. The lesions of the disease predominantly occur in particular areas of the tooth and their type is determined by the morphology of the tissue in which they appear.

"The acids involved in the carious process are derived from carbohydrate substrate after they have been acted upon by microbial enzymes. The enzymes have their origin from the microbial flora which has an enzyme system capable of breaking down carbohydrates to acids. Any microorganism or combination thereof, which is capable of maintaining an acid potential sufficient to decalcify enamel, is capable of initiating dental decay.

"The following microorganisms have been found capable of producing acid potential in vitro: Lactobacilli, aciduric streptococci, diptheroids, yeasts, Staphylococci, and certain strains of sarcina. The lactobacilli have been the only microorganisms which have been found to show a significant increase in incidence with the initiation of caries. Lactic acid has been demonstrated to be present

in the carious lesions by a specific method. Phosphoglyceric, pyruvic, formic, acetic, proprionic, and butyric acids have been demonstrated to be formed by microbial action in saliva sugar mixtures.

"Whether or not the acid formed will decalcify the enamel of the tooth is dependent upon: (1) the degree of acidity; there is good evidence to indicate that an acid potential in the vicinity of pH 5.0 is sufficient to decalcify the inorganic structure of a tooth, (2) the time that it is in contact with the tooth; the time that the acid must be in contact with the tooth in order to produce decalcification is not known.

"A suitable substrate and enzyme system are necessary for the production of acids. The preponderance of evidence indicates that the acids are formed by the presently accepted "anerobic phase" of carbohydrate degradation. We recognize that other paths of degradation are possible but as yet have not been demonstrated to occur in the mouth. The substrate is derived from ingested carbohydrate or carbohydrate from any other possible source. The enzyme systems are known to be derived from the microorganism, but they also may be derived from the oral tissues and secretions.

"The effect of the process on the tooth (carious lesion) is made possible by circumstances or structures which retain sufficient acid in contact with tooth substances. These include: (1) the dental plaque (an organic nitrogenous mass containing multitudes of microorganisms firmly adhering to the teeth), (2) anatomical characteristics of the teeth, (3) the position or arrangement of the teeth in the dental arch, (4) dental appliances. The above are not necessarily in their order of relative importance.

"There are also natural factors in the mouth which contribute to the dissipation of acids formed on the tooth surface such as: (1) the amount of saliva, and (2) the buffering capacity of the saliva. A few reports have suggested that resistance to dental caries in human beings may be accounted for by inhibitory substances. Until such time as more evidence is available to indicate the identification and action of these factors, it is necessary merely to recognize their possible role.

"The determining factor as to whether or not the carious lesion is developed depends upon the interrelationship of all the above variables, so that *no single factor may be construed as being the general cause of all dental caries. . .*"[1]

One fact stands clear from this definition and that is that the acid formation is a localized reaction occurring at the site of bacterial concentration which does not appreciably change the relative acidity or alkalinity of the whole saliva.

The microorganisms involved in this process are almost universally found in the mouth in varying numbers. If conditions are suitable and there is sufficient media for growth, these microorganisms will be found in extremely high numbers. Obviously, if there are greater numbers of bacteria capable of reproducing acids from carbohydrate food substances, there will be a greater concentration of acid immediately after ingestion of sugar. Also, if there is a greater ingestion of sugar in a mouth containing large numbers of bacteria there will also be a greater concentration of acid.

It has been demonstrated that this acid is formed within three minutes after the introduction of carbohydrates,[2] reaches a peak of formation within fifteen to twenty minutes, and remains for an hour or more. During this period, damage to the teeth may occur. After periodic repetitions of this process over a period of time, cavities develop and progressively enlarge. The simple sugars, monosaccharides, and disaccharides, are of most concern since they are most rapidly converted to acid under the conditions present in the mouth.[3] Starches are also to be considered inasmuch as the saliva contains an enzyme, ptyalin, capable of breaking starch down to a sugar. This is a slower process, however, and is only concerned in the caries process if starch foods remain in the mouth for a period of time.

Therefore, the amount and frequency of ingesting the carbohydrate substrate and the numerical presence of acid-forming bacteria will determine the rate at which these acids are produced.

Thus with this understanding of the carious process, we can realize that dental caries differs from any other bacterial infection affecting the human body in that it occurs within the oral cavity and outside of the bodily tissues that are capable of inflammatory reactions.

Several routes of attack can be considered in the control and prevention of this disease. One, of course, is the repair and restoration of the damaged part of the tooth while the lesion is small, thereby preventing its progression. Second, is the elimination or control of the carbohydrate foods responsible. Third, is the elimination of the carbohydrate foods from the mouth immediately after eating. Fourth, is the neutralization of the acids as soon as they are formed. Fifth, is the elimination or reduction in the mouth of the microorganisms responsible for the acid formation. Sixth, is the inhibition of one or more phases of the chemical reaction involved in the formation of acid from carbohydrates. Seventh, is the development of a surface tooth structure that is more resistant to acids. Eighth, is the treatment of faults in the tooth structure so that these weak spots are less permeable to the penetration of microorganisms or acids.

Each of these will be discussed as to their practicability and point of development.

Restoration of damaged tooth structure is the only sure way of treating a cavity that has already formed. If the restoration is complete and all carious tooth structure is eliminated as taught by Dr. G. V. Black at the turn of the century, there is reasonable assurance that the lesion will not progress. Complete restoration of all carious lesions is therefore the first step in the control of dental caries for the child patient. Historically speaking, dentistry is now in the restorative period and the remaining preventive methods are now being developed for widespread use in the practice of the future.

The elimination of the substrate (carbohydrate foods, especially refined sugars) in the diet is the basic principle for preventing the initial carious lesion. Herein some interesting figures from the Department of Agriculture give us an insight into why dental caries has become an increasingly widespread disease of children.

The consumption of free sugar has increased in the United States from 17 pounds per person a year in 1824 to approximately 95 pounds per person in 1948. The total consumption of sugar has increased since 1823 from a few thousand tons to more than 500,000 tons. In 1927 the total consumption of candy was 1,733,000,000 pounds or a per capita of 14.7 pounds. In 1943 the total consumption was 2,561,000,000 pounds or a per capita of 19.0 pounds which was sold for a total of 336 million dollars. However, candy alone is not the only problem. There are many foods and confections available that are as rich in refined sugar as candy or richer. Some of these are soft drinks, canned fruits, pastries, and many others.

However, the amount of sugar in each item is not as important as is the time and method of consumption, and how much remains in the mouth. If sugars are consumed only at mealtime together with a well-balanced and adequate diet, there will be a greater elimination and dilution by the other foods, saliva, and the act of mastication. On the other hand if a small amount of sugar is consumed regularly between meals such as may be obtained from cough drops, chewing gum, cookies, raisins, cough syrups, or soft drinks, there is a greater possibility of localized acid formation without disturbance. One case history of a child, aged 23 months, who was encouraged to eat and suck raisins at any time and to excess, showed that he had some thirty separate carious lesions. Another is a case of a patient, aged 4 years, who had developed eight carious lesions in a period of five months during which time she had been instructed to suck on a cough drop at bedtime to control a chronic cough of unknown origin. Another case is that of a patient, aged 2 years, who had been weaned from the bottle by means of a stick of peppermint candy in order to aid him to go to sleep after feeding. He presented a clinical picture of two exposed and abscessed teeth and some twenty-five separate carious lesions. Another interesting case is that of an 18-year-old boy who had a history of complete inactivity of caries throughout his life. After graduation from high school, he went to work with a construction gang for three months and during that time consumed two bottles of a cola beverage a day with the other workmen. This he had never done before while in school, and, at the end of the three-month period, he had developed nine clinically evident carious lesions. There are numerous other patients who present similar histories that, although they are clinical histories and not controlled research studies, serve to emphasize the importance of this side of eating habits.

This method of sugar consumption is vicious in that it has developed into a great habit for American children, that of eating, drinking, sucking, or chewing on something almost continuously between meals. The delicacies most readily available and most highly advertised, of course, contain sugar in varying amounts and are most often given to children by kindly adults who have no regard for regular eating habits.

Another fact to be considered is the more extensive use of canned fruit and fruit juices in substitution for fresh fruit which provide an added source of sugar. All of these serve to cultivate an artificial appetite and craving for sugar by the child which, once started, is difficult to break. Trained nutritionists

will tell you that an adequate diet may be planned without *refined* carbohydrate and still maintain a high daily calorie intake. Therefore, with this in mind, our interest in caries prevention becomes more intensely focused on dietary control, and depends more upon parental education.

Elimination of the substrate from the mouth immediately after its introduction is centered around oral hygiene. By brushing the teeth immediately after the consumption of concentrated sugars and starches, a great deal may be accomplished in the prevention of the initial lesions of caries.[3] Or, if this is not possible, the practice of rinsing the mouth with water at this time by forcing the water between the teeth with the tongue and cheeks is a good hygienic measure. The effectiveness of this method of caries prevention depends again upon the time and thoroughness of the oral hygiene. Certainly the mouth should be thoroughly brushed after each meal and after the eating of sugar foods and before retiring at night, provided that nothing is eaten afterward. For most children, oral hygiene is not very adequately carried out, but the habits should be developed at that time. Parents should be instructed to brush the young child's teeth regularly. A proper technique should be taught that is simple and yet reaches every possible space where food might lodge.

Neutralization of the acids as soon as they are formed is a means of caries prevention provided by nature.[3] The saliva is normally alkaline and very highly buffered. This is the factor that makes up the individual differences which allow the next door neighbor to get away with high sugar consumption and yet not have caries while you consume less sugar and have caries. By varying the amount of alkaline ash foods in the diet, the buffering capacity of the saliva may also be altered.[4] Therefore, in an effort to increase the buffering capacity of the saliva, a greater amount of fresh fruit and green vegetables should be consumed daily. These foods also provide a good cleansing action during mastication.

The elimination or reduction in numbers of microorganisms is a positive approach to caries prevention, but a difficult one. Elimination of the substrate is one method which reduces the bacterial flora concerned. Fluorides may play a part in this also. However, this action of fluorides is yet unconfirmed.

One method of reducing acid-forming bacteria in the mouth has been given a great deal of publicity recently and has taken the country by storm—that is, the ammonium ion dentifrice. It has been demonstrated to be very effective in the matter of reducing oral bacteria,[5] but has not yet been proved actually to reduce the incidence of dental caries, or to be more effective in this than an ordinary dentifrice when used after meals. Studies now nearing completion should give evidence to these facts that will clarify this issue. Until this information is released, however, these dentifrices are only licensed on an experimental basis. Many are on the market that are not licensed and are making unfounded claims for their product with misleading advertisements. In this way, many dentifrice manufacturers are taking advantage of the situation and the public in order to sell their product. This can certainly lead to embarrassment and confusion if the expected results are not significant enough to be of value.

Recent reports on the use of chlorophyl[6] in caries prevention are even more in their infancy, but act in the same manner by reducing the numbers of microorganisms in the mouth.

Interference with the mechanism of sugar reduction to acid is a method that may provide a measure of caries control in the future. One study reported the use of vitamin K in this capacity.[7] Other studies are now under way to find a substance of this type to include in commercial sugar preparation in a manner similar to the way iodine is used in salt preparations.

The topical application of sodium fluoride and the introduction of optimum amounts of fluorine in the public drinking water attempt to prevent caries by means of developing a surface enamel that is more capable of resisting dissolution by acid. It has been known for a long time that there is an inverse relationship of the incidence of dental caries to the amount of fluorine in the public water supply.[8] The optimum amount of fluorine for caries prevention without danger of dental fluorosis (mottling of the teeth) is one part per million. Studies are now in progress that will attempt to prove this effect by artificially adding fluorine in the above amount to water supplies not naturally containing this element, without toxic accumulative effects upon the users of such water. Recent studies by the United States Public Health Service[9, 10] and other research teams have shown that the topical application by a dentist of a 2 per cent solution of sodium fluoride may be of value in caries prevention. This has been shown to be approximately 40 per cent effective by a statistical analysis of a large group of children treated. There are many questions about this unanswered as yet, that have led many dental research men to cast disconcerted looks at the unlimited publicity given this method of caries prevention. Nevertheless, it has been adopted and recommended by the American Dental Association and the Illinois State Health Department as an accepted type of dental treatment.

The last method of caries prevention involves the use of certain drugs, such as silver nitrate and zinc chloride to block uncalcified faults in enamel to prevent the ingress of acids or microorganisms into dentin and thereby make the tooth more resistant to dental caries.[11] This also is a very immature phase of caries prevention that may or may not have future possibility, although it has been given several big write-ups in national magazines as an effective caries prevention treatment. The studies that have been reported to date on this are inconclusive and must be continued before any information of any value can be released.

Several practical methods of caries prevention and maintenance of oral health may be set down that apply to every child patient in the form of daily rules.

These are:

1. Reduce the total daily intake of refined sugars and soft starches.
2. Eliminate daily between-meal and before-bed snacks of foods containing refined sugars or starches.
3. Increase the daily intake of rough foods, fresh fruits, and green vegetables.

4. Practice oral hygiene measures after every meal—either thoroughly brushing the teeth or rinsing the mouth with water.

5. Use an ammonium ion dentifrice. It costs little more than a regular dentifrice, does the same job, and may be proved to be of value in caries prevention in the near future.

6. Accept the topical application of sodium fluoride as a possible aid that may be of value and apparently can do no harm.

7. Last, and probably the only approach a dentist can control, have all cavities already developed restored when they are small, deciduous and permanent teeth alike. A regular and periodic visit to the dentist is required for this, and the number of new cavities developed each year will vary with the degree of cooperation obtained in the first four rules.

All of these rules apply to parents, children, and dentists. There is also a set of suggestions that a pediatrician or family physician can present for patients which will help form the basis for a good prevention program.

These are as follows:

1. Avoid endorsing lollypops, chewing gum, or confections in general by giving them out to children as rewards at the end of an appointment. This may break down all the control that a parent has with a child in avoiding these habits as well as to put the dentist in an embarrassing position.

2. Avoid the use of medications or dietary supplements, when possible, containing sugar, syrup, or honey as vehicles. This is especially important when they are to be used repeatedly over long periods of time, even if individual amounts are small.

3. Avoid indiscriminate recommendations of between-meal eating of sugar foods when possible to do otherwise.

4. Control diets of long-hospitalized patients so that they are low in refined sugars and soft, mushy starches and high in fresh fruit and green vegetables in addition to being well balanced.

5. Instruct nurses to provide oral hygiene measures after meals for hospitalized cases.

6. Instruct parents to take their children to see a dentist interested in children and preventive dentistry as early as 2½ years of age.

7. Recognize when children are getting proper dental care and consult with the dentist involved when question arises.

8. Instruct parents early as to what factors are involved in dental caries and dental disease and what measures they should take to prevent it. This should be well understood by parents when the child is one year of age.

9. Aid the dentist when asked in the planning of a diet for a patient of extreme susceptibility that meets the above requirements.

These suggestions will greatly aid the parents in planning good dental health for their children and will also serve to emphasize suggestions already made in schools and dental offices. Dental caries is not just a problem for the dentist

to be concerned about. It is, rather, a problem for everyone and anyone who has anything to do with health and education. At the present time, the dentist is kept so busy repairing damage already done that he takes little time to discuss these matters with parents. Maybe a concentrated effort on the part of teachers, parents, physicians, and dentists will provide this obvious gap in preventive medicine with an adequate stopper.

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# DOES MODIFIED MEASLES RESULT IN LASTING IMMUNITY?

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THERE are three ways by which the answer to this question might be obtained. The first is to administer to individuals who previously had modified measles a challenge infection with cultured measles virus, with nasal secretions or with blood obtained from patients with active cases of measles. The second is by deliberately exposing such persons to active measles under field conditions, and the third is to analyze the experiences of a large number of physicians who have seen a great quantity of measles cases. The difficulties of the first two methods are obvious.

The third procedure seemed most expedient and so 500 questionnaires were sent to pediatricians throughout the United States, and to a few in Canada, Mexico, France, South America, and Sweden. The first 250 were sent to individuals who were known by their writings to have been interested in measles prophylaxis, infectious diseases, and in epidemiology, to heads of departments in medical schools and large hospitals, and to some pediatricians known to have large practices. The next 250 were sent to every third pediatrician listed in the directory of the American Academy of Pediatrics.

An additional group of more than 500 physicians were canvassed by the author. These were members of the Pediatric Staff of Mount Sinai, and the Willard Parker Hospitals of New York, members of the New York Pediatric Society, and pediatricians attending meetings at the New York Academy of Medicine during the 1948-1949 season and the Academy of Pediatrics in Atlantic City in 1948, and the combined groups attending the 1949 meetings of the Society for Pediatric Research and the American Pediatric Society, and other pediatric groups. Many general practitioners were also questioned. Several of the heads of pediatric departments were kind enough to ask members of their staffs to add their own experiences. The New York City Health Department of Epidemiology was also consulted. Finally, information was sought from the Lederle Laboratories, E. R. Squibb & Sons, and Cutter Laboratories, and from the American Red Cross, about the amount of gamma globulin distributed, and their experiences.

The written returns number 166 and represent a much larger number of pediatricians, since some heads of pediatric departments indicated that the answers represented the experience of the entire departmental staff. The data acquired by letter and by personal contact probably represent the experience of approximately one-fourth of the pediatricians of the United States, and about one-third of those in New York City. Written answers came from nineteen states, from Mexico, Cuba, Canada, Chile, France, England, and Sweden.

From the Department of Pediatrics, Mount Sinai Hospital.

Only nineteen physicians indicated that they had observed measles in 29 individuals who had previously had modified measles. Four of them accounted for 12 cases of which 8 were probably authentic second attacks of measles while the data for the other 4 are not convincing. The data offered for 3 of the remaining 17 cases are difficult to evaluate and are therefore questioned. Detailed account of 27 of the 29 cases is presented in Table I. Six additional pediatricians believed that they observed measles subsequent to modified measles but had no records of the cases and could not recall them accurately. Two indicated that they had seen, "quite a few cases of measles following modified measles." Six pediatricians indicated that they had observed regular measles twice in the same patients some years apart. Dr. H. Hodes[1] saw a 9-year-old boy with typical measles in 1946, three years later in 1949 this boy had another attack of unmodified measles. The second attack occurred when the boy's general resistence seemed to have been lowered by repeated infection.

Of some interest is the fact that of the nineteen physicians reporting measles following the modified disease, four describe multiple cases in their own families or in other families. Can there be some familial pattern of immunity, or does this mean that we physicians have been conscious of recurrent measles in our own or friends' families and have missed these recurrences in other groups?

Measles occurred as early as seven months and as late as fourteen years after the attack of modified measles. There seemed to be no definite correlation between the severity of the modified measles and the subsequent measles, 19 of the 22 having developed moderately severe or very severe measles after the very much modified illness. Only one patient had very mild measles after a moderately modified disease. Possibly too few cases were reported to draw definite conclusions in this regard. The cases of modified measles were described as slight, mild, moderate, while the attacks of measles were described as moderate, usual, typical, severe, and very severe.

Several answers to the questionnaire contained statements of opinion but no observations to back these impressions. There were about as many who felt that modified measles rendered a person immune as there were those who suggested that they expected to see measles follow modified measles, especially after the very much modified illness. The data already presented indicate that permanent immunity is not universal subsequent to modified measles, but they also indicated that lasting immunity is probable in most persons.

There is considerable additional evidence to the information recorded so far, suggesting that modified measles renders a person immune. Measles prophylaxis has been practiced on an increasing scale since 1920. Convalescent serum (Nicolle, Conseil, and Degkwitz[2]) was followed by immune adult blood serum (Rietschel[3]). Placental globulin (McKhann and Chu[4]) was widely used from 1934 to 1944. A fractionated blood plasma preparation containing all globulins was introduced in 1934 (Karelitz[5]) and this product was distributed at the New York City Health Department serum laboratory when convalescent serum was not available. Since 1943 gamma globulin has been used on a large scale. The New York City Health Department makes gamma globulin available without charge

TABLE I. MEASLES REPORTED TO HAVE OCCURRED IN PERSONS WHO PREVIOUSLY HAD HAD MODIFIED MEASLES

| NAME | MODIFYING AGENT* | MODIFIED MEASLES | AGE AND DATE MODIFIED MEASLES | AGE AND DATE SUBSEQUENT MEASLES | NATURE OF MEASLES | COMMENT† |
|---|---|---|---|---|---|---|
| Se-b | C.S. | Not sick, scant rash | 1928 | 1938 | Usual moderate | PC |
| CC-C | C.S. | Very mild, Koplik's | 14 yr. | 16 yr. | Usual moderate | PC |
| AC-C | C.S. | Very mild, fever | 12 yr. | 13 yr. | Usual moderate | PC |
| JV-c | C.S. | Very mild, rash | 5 yr. | 7 yr. | Usual moderate | PC |
| LC | 5 c.c. C.S. | Moderate modification | 2 yr., 1938 | 11 yr., 1947 | Severe | PC |
| AP | C.S. | Moderate Koplik's | 7 yr., 1941 | 9 yr., 1943 | Severe | PC |
| MC | 20 c.c. W.B. | 102° F., one-day rash, no Koplik's | 2 yr., 1932 | 5 yr., 1935 | Average | PC |
| SP | G.G. | Very mild, "faint rash" | 6 yr. 4 mo., 1948 | 6 yr., 11 mo., 1949 | Average | PC |
| AK | C.S. | Mild rash, Koplik's, 101° F. | 5 yr., 1928 | 6 yr., 1929 | Severe | PC |
| Dan | C.S. | Moderate | 11 yr., 1928 | 25 yr., 1942 | Mild typical | PC |
| Bert | C.S. | Mild | 9 yr., 1928 | 23 yr., 1942 | Severe | PC |
| Fran | C.S. | Mild | 12 yr., 1928 | 26 yr., 1942 | Very severe | PC |
| Annie | C.S. | Mild | 5 yr., 1928 | 19 yr., 1942 | Very severe | PC |
| GYO | 20 ml. W.B. | Mild, Koplik's | 2 yr., 1942 | 1944 | Mild but typical | PC |
| GR | 2 ml. G.G. | Rash, Koplik's (?) | 7½ yr., 1947 | 9½ yr., 1949 | Moderate, no cough | PC |
| Rad | None | Mild | 3½ mo. | 3 yr. | Severe | Possible modification at 3½ mo. of age |
| Rad | 2 c.c. G.G. | Mild | 4 yr. | 7 yr. | Severe | PC |
| MKS | I.A.S. | Mild rash, Koplik's | 2½ yr. | 6 yr. | Severe with encephalitis (?) | PC |
| FWT | G.G. | Attenuated | ? | Years later | Typical | PC |
| MS | 4 c.c. G.G. | Faint rash, fever 2 days, cough | 6 yr., 1948 | 7 yr., 1949 | Typical | PC |
| HC-b | C.S. | Doubtful, no illness noted | 1928 | 1934 | Usual moderate | Records inadequate, case very unlikely |
| JC-b | C.S. | Doubtful, no illness noted | 1928 | 1934 | Usual moderate | Records inadequate, case very unlikely |
| ED-w | C.S. | Very mild reaction? Questionable measles | 4 yr., 1935 | 11 yr., 1942 | Typical | DC |
| MD-w | C.S. | Very mild reaction? Questionable measles | 2 yr., 1935 | 9 yr., 1942 | Typical | DC |
| LP | 17 c.c. I.A.S. | Temp. 99°-100° F., no rash, no catarrh, no Koplik's | 2½ yr., 1934 | 3½ yr., 1935 | Mild | DC |
| LP | C.S. | Very mild | 9 yr., 1927 | 10 yr., 1928 | Doubtful | Very doubtful |
| CRH | G.G. | Mild cough, Koplik's | Feb. 3, 1947 | March 16, 1947 | Rash, chest and abdomen, no fever, cervical adenopathy | Probably not measles second time. Rubella (?) |

*W.B. = whole blood; C.S. = convalescent serum; G.G. = gamma globulin; I.A.S. = immune adult serum.

†PC = Probable case; DC = doubtful case.

Note: C. F. McKhann has observed two instances of measles following modified measles. His records were not available for more data.

for any exposed susceptible child under 5 years of age. Prior to the introduction of gamma globulin it had distributed the products currently popular for measles prophylaxis.

The extent of the practice of measles prophylaxis is indicated by some of the letters I have received and from information obtained from pharmaceutical firms and the American Red Cross. A statement from one of the pharmaceutical firms[6] noted that in 1940, a representative year, 2,530 — 2 c.c. vials and 480 — 10 c.c. vials of immune globulin were distributed. Another[7] reported that to date (October, 1948) approximately 2,500 liters of immune globulin and 400 liters of the newer alcohol fractionated gamma globulin have been distributed. Taking 3 c.c. as an average dose of the first preparation and 2 c.c. for the gamma globulin, well over a million doses were distributed. About 200,000 doses of gamma globulin have been distributed by this one firm, and there are six firms preparing gamma globulin from Red Cross blood. Dr. Louis K. Diamond,[8] medical director, National Blood Program for the American Red Cross wrote that up to June 3, 1949, and for the previous five years, 1,819,702 units, mostly in 2 c.c. vials of gamma globulin were distributed ,and that New York City alone received 128,000 units in that period. McKhann[9] wrote that his group had administered immune globulin to 4,000 persons to produce modified measles. Dodd[10] stated that she had seen well over 100 cases of modified measles. Sako[11] has given gamma globulin to about 200 children. Jacobson[12] and Parmelee[13] answered that they had administered all available prophylactic agents since the introduction of convalescent serum, so have many others whom I interviewed personally. Yet of all of the above mentioned only McKhann knows of two instances of measles occurring years after these patients had had the modified disease, and the remaining physicans canvassed saw only 20 definite cases.

My own interest in measles prophylaxis dates back to 1925. As part of my studies I have administered the various prophylactic agents to a large number of children, more than 2,000. In most cases I have been able to observe the results. Many of the children who had modified measles are still my patients or are available for questioning. When questioned, 25 of 26 of them indicated that they had been exposed to measles at least once in the five to fifteen years subsequent to the modified attacks and remained well. Only one instance of measles occurring one year after an attack of modified measles was observed by me in 1926. One other child, a patient of mine, who had had modified measles in 1941 is supposed to have had measles in 1944, but the description of the second illness leaves considerable doubt that it was due to measles.

Further evidence suggests that a long enduring immunity follows modified measles. In the fifteen years between 1933 when placental globulin first became available and 1948, there were reported to the New York City Health Department[14] a total of 359,857 cases of measles. It is estimated that the actual number of cases of measles which occur are almost twice as many as are reported. A conservative estimate would place the actual number of cases of measles at one and one-half times the number reported or roughly 540,000 cases of measles; about 36,000 per year. Since 95 per cent of the adults of a cosmopolitan city

like New York have had measles in childhood, it implies that 95 per cent or more of the population have been exposed within a twenty-one-year period. Since the secondary attack rate is estimated at about 83 per cent,[15] the difference between 95 per cent and 83 per cent, or 12 per cent should have had more than one exposure to measles during childhood. The aforementioned, if correct, indicates that a fair percentage of those who had modified measles in the past fifteen years have also been re-exposed to measles. Thus we may presume that they remained well, or that the second attacks did not come to the attention of the group of doctors surveyed.

The United States Public Health Service[15] has noted that the median incidence for measles for the entire United States for the period 1942-1946 was 603,376, for 1947 it was 655,967, and for 1948, 603,804. Assuming that the number of actual cases exceeds the reported cases, as in New York City, this indicates a total of about one million cases of measles annually. This makes the chance of re-exposure to measles considerable and the low incidence of second attacks quite significant.

Further suggestive evidence that modified measles renders a person immune to measles are the following. In hospital wards many children who developed modified measles were re-exposed once, and sometimes twice within the next month or two, yet I have never observed measles to reoccur under such circumstances. Our experience with nephrotics is exactly the same as the above. If they had had modified measles, deliberate or chance re-exposure failed to produce the disease. Likewise, children who for several years remained in orphanages must have had re-exposures to measles without acquiring second attacks. In his response to the questionnaire Stokes[17] wrote, "Orphanages and our school for the deaf are good places for such follow-ups and we haven't seen second cases."

My experience with the T. family is of particular interest. In 1938 M. T., age 8 years, was exposed to measles and given convalescent serum. She developed modified measles after a suitable (11-day) incubation period. Her brother, P. T., age 6 years, was therefore given convalescent serum which was followed by an attack of modified measles. V. T., the youngest child, age 1 year, was given convalescent serum twice, when her sister developed measles and two weeks later when her brother developed measles. She was given enough serum to protect her both times, and protection seemed to have been accomplished.

In 1946, V. T., age 9 years, was exposed to measles and given 2 c.c. of gamma globulin, after which she developed an attack of modified measles. Her sister and brother were again exposed and given no prophylaxis and neither of them became ill. Thus modified measles seems to have protected the older sister when her brother developed the disease two weeks later, and both she and her brother remained immune eight years later when exposed to measles introduced by the sister. Furthermore, having protected V. T., the younger sister at age 1 year did not leave her with immunity sufficient to withstand an infection eight years later.

The aforementioned data have indicated a trend for long-lasting immunity following modified measles. There are no comparable data in the literature to

that presented here, but the observations of Maris, Rake, Stokes, Shaffer, and O'Neil[18] are pertinent to the question of this study. "Twenty-two children who had been previously innoculated with egg-passage measles virus were exposed by chance, at various intervals up to one year from the time of their innoculations, to children with active cases of measles under field conditions. Three of these children developed typical measles, one developed mild measles, three developed an extremely mild disease distinguishable with difficulty as measles, and fifteen deveoped no disease. Twenty-four children who had been previously innoculated with egg-passage measles virus were exposed by challenging injections of blood from active cases of measles at various intervals from the time of their original innoculations. Three of these children developed typical measles, two developed mild measles, five developed an extremely mild disease distinguishable with difficulty as measles, and thirteen developed no disease. One additional child showed a slight nasopharyngitis without fever, rash, or Koplik spots."

In a more recent paper Maris, Gellis, Shaffer, Dunham, Stokes, and Rake[19] have reported that of 386 children previously innoculated with measles virus, 69 per cent had contracted measles under home exposure in the next four to twenty-one months. Of a group of 24 children who were injected with normal allantoic fluid, 20 developed the disease on field exposure.

The type of measles produced in these children by the egg-passage measles virus resembles measles modified by prophylactic sera and globulin preparations after natural exposure to the disease. Yet, when challenged by reinjection of egg-passage measles virus, or by exposure under field conditions, an appreciable number developed mild measles and few, moderate measles.

Since there is no practical way of measuring relative degrees or qualitative differences of immunity induced by the disease following injection with the egg-passage virus against modified measles, it may not be warranted to conclude that because complete or permanent immunity to measles was not produced in some individuals by egg-passage virus that the same is necessarily true of modified measles. Indeed the evidence at hand suggests that the opposite is true.

Description of more experiences will be forthcoming now that the medical profession, especially the pediatricians, have been aroused to think of this problem. We must await further reports before final answer to the question can be given. From the data accumulated the following conclusions seem warranted.

1. The attempt made in this study to answer the question, "Does modified measles produce lasting immunity?" can be answered tentatively in the affirmative for most individuals.

2. The severity of the second attack of measles does not seem to be dependent on the degree of modification originally produced.

3. The possibility of familial patterns of immunity is suggested by the data.

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# SOME DEBATED POINTS IN THE TREATMENT OF ACUTE POLIOMYELITIS

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BEFORE presenting some points in the treatment of acute poliomyelitis that are frequent subjects of discussion, it is well to note that the Therapeutic Trials Committee of the Council on Pharmacy and Chemistry of the American Medical Association has recently published an authorized report on "Methods of Clinical Study and Evaluation of Therapeutic Agents in Poliomyelitis."[1]

This report showed that among the variables which must be controlled in any investigation of the efficacy in this disease of a therapeutic agent or procedure, are the following:

Variations in diagnostic criteria
Unpredictability of the course of the disease
Unpredictability of the outcome
Effects of different immunologic types of the virus
Effects of climatic and geographic variations
Age distribution of patients
Variations in techniques of applying treatment
Variations in measuring and judging extent of paralysis, deformity, and disability

Because of these many variables it is obviously necessary to have controlled observations of a very large number of patients to obtain an authentic evaluation of the effect of a particular therapeutic procedure in poliomyelitis. This is difficult to achieve and often impossible. However, able clinicians who have observed hundreds, even thousands, of cases over the years develop impressions of what is worth while and what is not; and at times equally experienced and intelligent observers have come to opposing conclusions. While recognizing that in many moot points what is right and best can be determined only after further research and study, one should find value, nevertheless, in stating some of the pros and cons, particularly concerning treatment procedures. Up to April 22, 1950, the United States has already had 1,449 cases spread across the country, or 27 per cent more than at this time in 1949. It would seem well therefore to discuss today those points which concern the practitioner, that he may perhaps be helped in caring for his patients this year, rather than discussing points which involve equipment and laboratory facilities that are not widely available.

First point: *Should all patients in early stages of the disease be transported to a hospital?* The obvious advantages of a hospital are: better care for the patient than can be given in most homes; more convenience for the doctor; and the greater availability of laboratory studies and of special equipment

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should its need arise. On the other hand, Horstman,[2] in New Haven, and Ritchie,[3] in England, have recently proved what had long been thought probable, that muscular exertion in the early febrile period aggravates the oncoming paralysis. And in at least two hospitals this past summer a study of patients in early stages of the disease transported great distances to the hospital compared with patients brought from the immediate neighborhood seemed to show an average of greater severity in the former group.

Good clinical care can often be provided in even modest homes, particularly since the best remedy at this time of fever is natural sleep. Unfortunately, there are still many hospitals that admit polio cases—usually as private patients—that have a little equipment such as a ringer and a respirator, but very little if any "know how," and where the patient is kept exhausted by overtreatment and unwise handling. During the febrile stage, the patient should be furnished a maximum of rest, comfort, and relaxation. For no purpose should he be awakened from natural sleep.

*Should a lumbar puncture be done invariably?* Before the onset of muscle weakness, and with signs of meningeal irritation present, examination of the spinal fluid is essential to rule out an early meningitis and perhaps to strengthen the diagnosis of poliomyelitis. But when the presence of paralysis and of other signs has made the clinical diagnosis obvious, the psychologic trauma and the physical struggle incident to the puncture may very well be more harmful to the patient's welfare than the information obtained is worth. Repeat lumbar punctures during the febrile period require a good bit of justifying.

*Shall the patient be deliberately dehydrated, and if so, how? What are some of the facts?* At autopsy, when death has occurred in the first week and even later, the weight of the brain is practically always appreciably greater than the average for the age period, the increase being principally due to cerebral edema, even though the eye grounds do not show choking of the discs. Also in the cord, capillary circulation, and with it the blood supply of oxygen to the anterior horn cells, is disturbed by petechial hemorrhages and the choking of perivascular infiltration and interstitial edema. Certainly, to quote Janeway,[4] dehydration (or something) is able to make dramatic clinical changes in cases where there is intracranial edema. In bulbar cases, overhydration may increase flooding of the pharynx, whereas dehydration helps to restrict the amount of fluid that must be removed.

On the other hand, some believe that a state of "shock" with diminished cardiac output is enough of a danger to warrant combatting dehydration; also, that slow drip administration of 10 per cent glucose does not dehydrate. Stronger glucose solutions do dehydrate but there may be a rebound. Some prefer to use irradiated plasma, concentrated two and one-half times. Johnston,[4] at the Henry Ford Hospital in Detroit, is convinced that dehydration is beneficial, and Elam,[5] in Minneapolis, advises that the specific gravity of the urine be kept between 1.025 and 1.030. Wright,[6] at Leetsdale, Pa., routinely uses 10 per cent glucose for its apparently beneficial results and this was also our routine procedure at the Knickerbocker Service in New York, where, it has

been reported before,[7] of the last twenty-three bulbar cases we lost only one. An additional patient, admitted at night in coma and dead in about three hours, may also have been suffering from bulbar poliomyelitis. The attractive hypothesis, of course, is that these effects are produced by true dehydration although the mechanism may be something else. Unless one makes elaborate studies of blood volume, it would be hard to know if dehydration occurred.

As to medications for various purposes, there are of course many opinions and many preferences, but there are also some facts. No antibiotic is known to affect the poliomyelitis virus, but penicillin is given routinely by some authorities to prevent secondary infections as of the lungs. As to sedatives and analgesics, many believe these are necessary to combat the discomfort and pain so common especially in the early days, and to permit the patient to get some sleep. Others recognize, however, that in a case of polio that is progressing, breathing difficulty may in a short time develop to proportions where conscious effort is necessary to carry on the act of respiration. If artificial sleep has been induced, death may occur while the patient sleeps. In the acute, progressive case, it is safest to forbid artificial sleep. Certainly, in each case, the relative advantages and disadvantages of such medication must be appreciated and carefully evaluated.

As to drugs intended to relieve muscle tightness and pain, Priscoline, a sympatheticolytic drug, has been warmly advocated, but it has not been tried in an adequately controlled study on alternate cases. Last summer at the Willard Parker Hospital it was given for a time to all patients in one ward and to none in an adjacent ward, mild spinal cases being admitted alternately to the two wards, and the house staff had the impression that if the drug was given in large enough dosage to produce flushing of the skin, the patients did receive benefit from it. It has not had wide acceptance, nor has intravenous novacaine, nor curare, nor Prostigmine. Curare, which erects a barrier at the motor end plates to certain of the stimuli coming from the brain, may have a field of usefulness for the patient who is struggling to breathe against a respirator by knocking out the impulse to breathe. Prostigmine, which lowers the barrier and is curare's antidote, probably has its greatest usefulness in polio by stimulating intestinal peristalsis just before an enema. For the muscle twitches and actual cramps that in occasional patients are a cause of considerable discomfort, quinine is being used more and more commonly, and with usual benefit.

For urinary retention there are sharp differences of opinion as to the use of catheterization and the early establishment of tidal drainage, or the use, as recommended by Lawson,[8] of such a drug as furfuryltrimethylammonium iodide which is marketed under the name of Furmethide. In allergic patients this drug can cause unpleasant side effects such as chills, sweating, and even bronchospasm, and furthermore, in possibly a third of the cases, the usual dosage is ineffective. Atropine, however, is a good antidote for the bronchospasm, and Furmethide is often enough effective for urinary retention to warrant its use

when needed in selected nonallergic patients. An objection to the use of an indwelling catheter is that it tends to prolong the period of urinary retention, and the risk of eventual infection is therefore increased.

The use of postural drainage is the subject of much dispute. A much quoted article[9] recently urged that the bed be tipped to 35 degrees to insure drainage of the trachea, presupposing that bulbar patients are maintained in a supine position as is usually done in a respirator. When the patient is in the side-lying position usually used for bulbar cases out of a respirator, or is prone, such an angle is not necessary, 20 degrees often being adequate. Some argue that a continuous head-down position tends to cause edema of the head, both inside and out, puffy eyelids, and increased choking of the discs having been described. These doctors would have the patients horizontal from 10 to 50 minutes in each hour, but other clinicians believe that the advantages of a moderate postural drainage, even continuous for several days, far outweigh any possible disadvantages.

There is general agreement that oxygen should be given freely to patients with bulbar involvements, as well as to those with any respiratory difficulty; also to those with apparent evidences of encephalitis because frequently the trouble is not encephalitis but hypoxia. Most clinicians believe in giving the oxygen by nasal instillation so as to leave the mouth free for the removal of secretions. It is not generally realized that if the oxygen is first passed through hot water in order both to moisten and to warm the oxygen, it is less likely to be irritating or to make the pharyngeal secretions stringy and inclined to cake. Small injections of saline or of sodium bicarbonate solutions into the pharynx or trachea during suction make possible a more rapid and easier removal of sticky mucus.

There is some variance of opinion as to the relative merits and uses of tank respirators, chest repirators, and the rocking bed, and in fact, as to when to start any artificial respiration. When the tank respirators were the only available means of mechanical artificial respiration, their obvious disadvantages made some of us reluctant and slow to put patients in them unless the indications were pretty strong. Many a patient with minor breathing difficulty could be carried along with oxygen and quiet and skillful nursing care until breathing was again free from any distress. Today if a rocking bed is available, and if the diaphragm is free from spasm and from encumbrance by abdominal distention, certain of these patients can well be carried along and rested by this gentle form of artificial respiration. Where hypoxia is sufficient to cause cyanosis, there is fairly general agreement that the tank respirator should be used promptly. A climbing venous plasma carbon-dioxide combining power above a normal of 62 volumes per cent is a good indication of a need for better ventilation. A decrease in the pH of the urine is also significant.

The chest respirator is convenient for transportation and for emergencies, but has definite disadvantages for prolonged use. The rocking bed is particularly useful for patients being weaned from tank respirators. Dr. Jessie Wright[10] of Leetsdale has probably had more experience with this type of arti-

ficial respiration than anyone, and has carefully defined the conditions and regulations that should govern its use. For greatest advantage from this type of artificial respiration, the chest and diaphragm must be pliable.

As to the use of differing pressures when the patient is in a tank respirator, a number of suggestions have been advanced by various authorities. Under most circumstances, a negative extrathoracic pressure of around 14 cm. of water is utilized, but most agree that the patient's maximum comfort should be the goal and the pressure adjusted accordingly. Some would force deeper breaths, perhaps for 5 minutes each hour, to keep the thoracic cage more flexible. Many advocate intermittent positive pressure breathing applied by mask or hood to the head or by special equipment to a tracheotomy tube, stating that the advantages are the promotion of bronchial drainage, more uniform alveolar aeration, protection against atelectasis, increase in lymph flow from the lungs, and the combating of pulmonary edema.

When, in comparatively rare cases, the breathing difficulty is due to failure of the respiratory center and a patient, usually semicomatose, breathes with irregular and shallow breaths but can on demand take a good breath, Sarnoff's electrophrenic respiration is apparently often effective in maintaining artificial respiration by action on one-half of the diaphragm. All spontaneous effort at respiration ceases with the onset of the phrenic nerve stimulation. But this apparatus and the requisite skill of operation are not yet widely available, and opinions differ as to what can otherwise be done. Some give curare enough to stop the motor impulses to the chest and let the tank respirator carry on. Some whip up the respiratory center if necessary with caffeine and oxygen, but aim to cut down the need for breathing by means of the utmost of quiet and rest.

As to the indications for tracheotomy, there are sharp differences of opinion. At the Los Angeles County Hospital where 3,094 cases were treated in 1948,[5] a so-called prophylactic tracheotomy was performed in 354 or a majority of their 603 bulbar and bulbospinal patients, both those eventually put in respirators and those not, and they reported a 19.4 per cent mortality of their bulbar and bulbospinal patients and an over-all mortality of 4.1 per cent. There are many other clinicians, particularly West of the Mississippi, who favor early tracheotomies, but most of the large clinics in the Eastern States use tracheotomies much more sparingly. For instance, the pooled figures of six hospitals[11] from Detroit to Boston show a total of 1,751 cases of polio admitted in 1949 with a mortality of only 3.2 per cent. Of these, 311 were bulbar and bulbar spinal cases, with a mortality of 15.7 per cent in contrast to the 19.4 per cent of Los Angeles. The six hospitals did only 19 tracheotomies of which 9 patients died. Over one-tenth of all patients admitted with poliomyelitis had tracheotomies in Los Angeles, but only about one in 100 had tracheotomies in the Eastern hospitals. Also, over one-half the bulbar patients in Los Angeles and about 6 per cent in the Eastern hospitals had this operation done. Van Riper,[6] the Medical Director of the National Foundation for Infantile Paralysis, noted in 1949, in his travels all over the United States, that there was generally a markedly lessened tendency to do tracheotomies from what he had observed in the preceding years.

The consensus of Eastern opinion might be summarized as follows:

I. *Indications for Tracheotomy in Poliomyelitis*
1. Bilateral abductor paralysis of the vocal cords. This causes a mechanical obstruction which must be by-passed.
2. Inability to keep the airway reasonably clear. Some clinics with good teamwork can be notably more successful in this than others that are overcrowded or have inadequate and untrained personnel.
3. Progressive hypoxia, not otherwise correctible.

II. *Advantages of Tracheotomy*
1. Easy removal of secretions from the trachea.
2. Ability to bronchoscope through the wound.

And if a proper oxygen attachment is available, which usually isn't:
3. Easier maintenance of adequate oxygen tension.
4. Easier treatment of pulmonary edema with positive pressure.
5. Easier to care for the patient.

III. *Disadvantages of Tracheotomy*
1. The operation at best is an ordeal to the patient who needs rest and a minimum of handling.
2. There are possible complications.
3. The mortality following tracheotomy in polio is high.
4. The tracheotomy tube narrows the airway and as a foreign body it increases intratracheal secretions.
5. Tracheotomy makes adequate oxygen administration difficult unless a proper oxygen attachment is available.

IV. *Conditions Occasionally Cited as Indications for Tracheotomy, but Which in Themselves Are Believed Insufficient Indications*
1. Inability to cough.
2. Inability to swallow.
3. Any laryngeal involvement besides bilateral abductor paralysis.
4. Pulmonary edema. This requires positive pressure artificial respiration, but besides through a tracheotomy tube, this can be given by mask, or by a hood on a respirator.
5. Atelectasis. This, we believe, requires immediate suction which can be better done visually by means of bronchoscopy than by blind suction through a tracheotomy tube.

Thus, most Eastern clinicians who see much acute polio believe that tracheotomy should be avoided if in any way possible.

A word might be added about the tilt-table which resembles a glorified seesaw that can be secured at any desired angle from horizontal to 65 degrees, head-up or head-down, with shoulder rests and foot rests. There is little if any practical use for the head-down position, but raising a patient to put weight on his feet who otherwise is too weak, too stiff, or too sore to assume other than a straight-lying position, is thought by some to have several marked advantages. The process of decalcification of the bones of the lower extremities may be slowed; the kidneys empty better and there may be a lessened tendency to the formation of renal calculi; a gradual adjustment of the patient's circulation to the change from the horizontal to a more nearly upright position may be accomplished; and finally, the patient is immeasurably benefited psychologically. It is believed that differences of opinion about the advantages of a tilt-table are due only to lack of experience with its use.

Finally, the older and more experienced the clinician, the greater and more unanimous is the conviction that the welfare of the acutely ill polio patient is best served by that expert medical and nursing care which gives earnest consideration to attaining complete rest and comfort of the patient. In Cecil's *A Textbook of Medicine*,[12] Paul has written, "In this particular disease one should guard the patient from meddlesome therapy," and he advised against "any procedures which will subject the patient to unnecessary strain." Thus, unnecessary tests and examinations should be avoided. If it disturbs the patient, the enthusiastic urge of the house-officer for study and research must be curbed, and thoughtful consideration of the patient should be substituted for the feeling that "you've got to be doing something."

But no one can justifiably claim to say with authority what is best in the treatment of acute polio. Such debatable points have been discussed as the advisability of moving patients in early stages of the disease long distances, of using dehydration, and of prescribing various sedatives and antispasmodics; the management of urinary retention; the use of the head-down position in postural drainage; the warming of oxygen; the use of artificial respiration; the pros and cons of tracheotomy; the advantages of the tilt-table; and the importance of the fact that treatment that is not indicated is contraindicated. Perhaps from the consideration of the pros and cons of these several points there may result a better understanding of the management of the acutely ill polio patient.

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# PRISCOLINE FOR PAIN IN POLIOMYELITIS

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IN ANY disease process where the etiology is unknown, and the treatment therefore nonspecific, efforts toward symptomatic therapy are made. According to Shaw and Thelander,[1] in poliomyelitis, "The early treatment of the paralytic stage is entirely symptomatic. . . . Early measures are suited only to maximum comfort of the patient and are accomplished by careful nursing, gentle handling, enforced recumbency, and protection."

Various drugs have been employed to control the pain, muscle spasm, tenderness, and hyperesthesias occurring in the acute stage of the disease. Such drugs have included the use of neostigmine[2] and curare.[3] The results, for the most part, have been equivocal. More recently, intravenous procaine,[4, 5] diethylaminoethanol hydrochloride,[5] and Priscoline hydrochloride have been used with promising success. This paper is concerned with the use of 2-benzyliminazoline hydrochloride (Priscoline*) in the treatment of thirty-seven patients with acute poliomyelitis during the summer and fall of 1949, at the University of Arkansas Hospital of the School of Medicine.

## COMMENT

Priscoline is an antagonist to epinephrine-like substances formed at the vascular myoneural junction. As has been shown by Smith and associates,[6] and by other workers in poliomyelitis, there is definite involvement of the sympathetic nervous system in acute poliomyelitis. Pathologic studies demonstrate varying degrees of involvement, not only in the anterior horn cells, but also in the sympathetic cells in the lateral horn of the spinal cord and in the sympathetic ganglia. Oscillometric studies have demonstrated angiospasm in the peripheral circulation in all forms of poliomyelitis. Indirect evidence for involvement of the sympathetic nervous system, such as urinary retention, pylorospasm, Horner's syndrome, constriction and/or dilatation of blood vessels in the skin, is observed in many patients. These vasomotor and sweat secretory disturbances have also been described by Kuntz.[8] Smithwick and others[9] have shown that lumbar sympathectomies in cases of residual paralysis were accompanied by accelerated rate of growth in the involved extremity. On the basis of this evidence, it has been presumed that the well-known findings of pain and spasm seen in acute poliomyelitis might be ascribed to the action of the virus on the cells of the sympathetic nervous system, either centrally or more peripherally. If this reflex spasm and pain could be controlled, patients not only would be made more comfortable, but it would allow the physiotherapist greater freedom. In this series of cases we have attempted to assay the effectiveness of

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Priscoline as compared with hot packs and the usual forms of analgesia. The opinions of the house staff, nurses, physiotherapy department, and attending orthopedists were carefully considered before final appraisal was made.

### DOSAGE AND ADMINISTRATION

Except in the early cases, all patients received increasing parenteral doses every three or four hours till flushing occurred; they were then maintained on the preflushing dose, either parenterally or orally. The initial dose varied with the size and age of the patient. In general, children under 5 years began with 10 mg. intramuscularly and this dose was increased by 5 mg. every four hours. Older children received 25 to 50 mg. as an initial dose and this was increased by 10 to 15 mg. every four hours. Wherever possible, it was attempted to maintain patients on an oral dose. The drug was stopped after another seven to ten days. In those where no appreciable effects were observed, hot packs were employed. In most cases, blood pressure readings were recorded before and after administration of the drug. All side reactions were noted. In general, bulbar patients were not given Priscoline because of the danger of adversely affecting blood pressures, which were already undergoing marked fluctuations as a result of the disease itself. In a few cases where there was spinal as well as bulbar disease, Priscoline was tried if the blood pressure was normal from the onset. Table I summarizes the distribution of cases.

TABLE I

| TYPE OF INVOLVEMENT | NUMBER | PER CENT OF TOTAL |
|---|---|---|
| Spinal | 30 | 83.3 |
| Spinal + encephalitic | 2 | 5.5 |
| Spinal + bulbar | 3 | 8.4 |
| Tetanus | 1 | 2.8 |
| Total | 36 | 100.0 |

### RESULTS

In any study where the results are almost entirely evaluated on the basis of symptoms such as pain, variable factors which cannot be controlled are automatically introduced. The following clinical impressions are tabulated according to whether patients were or were not benefited with regard to relief of pain and spasm, increased warmth in extremities, and greater ease of manipulation by the physiotherapist. In a certain number, the results could not be completely evaluated for a variety of reasons: patient left the hospital, unsuitable case, delirium, fluctuation blood pressure, etc. In a few, the results were equivocal, so they were classified as "doubtful benefit."

It will be seen by the figures in Table II that less than 25 per cent of the patients treated were definitely benefited by the drug, whereas almost 45 per cent of them were definitely not benefited. In three of the nine patients benefited, this occurred only following parenteral doses of the drug. Oral doses had apparently no effect. As a matter of interest, a patient with tetanus was given Priscoline to see if there would be any effect on the muscular rigidity. None was noted.

TABLE II

| RESULTS | NUMBER | PER CENT OF TOTAL |
|---|---|---|
| Benefited | 8 | 22.2 |
| Doubtful benefit | 4 | 11.2 |
| Not benefited | 16 | 44.4 |
| Not completely evaluable | 8 | 22.2 |
| Total | 36 | 100.0 |

## TOXICITY

Table III summarizes the undesirable side effect of the drug. It will be noted that the most important was the production of hypertension. It was the only side effect responsible for discontinuing the drug permanently in a given patient. One 18-year-old boy with spinal disease affecting all extremities and intercostals, showed disappearance of pain and tenderness on the fifth day of therapy; on the seventeenth day of therapy, he developed gastrointestinal bleeding and a gastric ulcer was demonstrated by x-ray. Some rise in blood pressure had also been noted. Whether the bleeding was the effect of the hypertension per se, or due to a disturbance of the autonomic nervous system by the disease process and/or the drug, is questionable.

TABLE III

| SIDE EFFECTS | NUMBER OF PATIENTS | | PER CENT OF TOTAL PATIENTS |
|---|---|---|---|
| | BULBAR | SPINAL | |
| Hypertension | 3 | 4 | 19.4 |
| Nausea—vomiting | | 3 | 8.3 |
| Pruritis | | 1 | 2.8 |
| Hypotension and Paresthesias | | 1 | 2.8 |

As is seen in Table III, seven patients showed a rising blood pressure while only one developed hypotension, even though, theoretically, this drug would be expected to produce a lowering of the blood pressure by virtue of its sympathicolytic action. Four of the patients had only spinal involvement and three had spinal plus bulbar disease. The drug was not given to bulbar patients who showed aberrations in blood pressure. The blood pressure in the spinal patients returned to normal soon after the drug was discontinued, but in one case it remained elevated for one month. The blood pressure continued to fluctuate in the bulbar case. Nausea and vomiting was seen in three cases, but in all three, the drug was resumed after a short period of rest with no further symptoms noted. One patient developed severe pruritis, and one hypotension with paresthesias over the entire body.

## SUMMARY AND CONCLUSIONS

1. Thirty-five cases of poliomyelitis and one case of tetanus were treated with Priscoline in an effort to reduce pain and spasm.

2. Less than one-fourth were definitely benefited; almost one-half were not benefited at all. The remainder were either doubtful or could not be completely evaluated.

3. This is a worth-while drug when it acts favorably; in our hands it is about as effective as other drugs and safer than some, especially curare.

4. Fluctuating blood pressure was observed in all cases where there was bulbar involvement. This was probably due to the disease itself, although hypertension was noted in four cases where there was apparently only spinal disease.

5. It was felt by all observers that hot packs proved superior in the relief of pain and spasm, in the majority of patients.

6. From the experimental and clinical evidence, it would appear that a sympathetic antagonist would be the drug of choice in the control of pain and spasm, especially if it could be given orally. Therefore, further study of such drugs is indicated.

The authors acknowledge the appraisals of this drug by the following house-officers who also observed these patients: John A. Harrel, Jr., M.D., Luther R. White, M.D., and Marion K. Ledbetter, M.D.

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# SERUM POTASSIUM IN POLIOMYELITIS

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LOW concentrations of serum potassium have been observed in a variety of conditions: familial periodic paralysis,[1] treatment of diabetic acidosis,[2] intestinal obstruction,[3] chronic nephritis,[4] sprue,[5] treatment of diarrhea,[6] patients receiving desoxycorticosterone,[7] and adrenal insufficiency.[8] The occurrence of normal or low serum potassium levels during paralyses has been demonstrated by a number of investigators.[1, 4, 9, 10]

The possible correlation between serum potassium concentrations and the amount of paralysis of poliomyelitis was studied during the summer and fall of 1949, at the University of Arkansas Hospital at Little Rock. The patients admitted to the wards of the hospital were usually in the advanced stages of the disease in which muscle spasm and paralysis had already become manifest and potassium levels were not obtained prior to the onset of muscle weakness or spasm.

In all, fifty-six cases were studied. Thirty-two of these are shown in Tables I-IV. Thirteen patients had no weakness or paralysis on discharge, twenty-nine had slight weakness of one or more extremities and were transferred to convalescent hospitals, twelve had severe paralysis involving several extremities or intercostals; in four the diagnosis was questionable, one died on the fourth day, and two others died in the fourth month.

Fasting-blood samples were obtained in all cases except for those drawn on admission; however, these patients usually had not eaten for from 4 to 6 hours prior to arrival at the hospital. The clinical determination used was the Hoffman method as described in Levinson and MacFate, *Clinical Laboratory Diagnosis*[11] and the flame photometry method was that of Overman and Davis.[12] The results shown are all flame photometer readings except those designated by asterisks which are chemical readings. The normal range was from 4 to 5.6 meq. per liter for serum potassium and from 137 to 160 meq. per liter for serum sodium. The spinal-fluid potassium range was from 2.2 to 3 meq. per liter.[13] In order to conserve space, only representative results are given.

In Table I are reports of nine patients in whom a diagnosis of poliomyelitis was made on the basis of clinical, spinal fluid, and orthopedic findings. The serum potassium was normal except for a slight elevation in the first patient. All patients were later discharged home and at the time of discharge, there was no evidence of muscular weakness or paralysis.

The cases recorded in Table II are of patients who all had serum potassium levels within normal range but who had some residual weakness or paralysis of isolated muscle group on discharge from the hospital, except one (Case 2) who died on the fourth day of the disease.

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Patients with low serum potassium readings are listed in Table III. There was no history of preceding vomiting or diarrhea to account for the low levels. All of these were severe except one (Case 10), in whom the diagnosis was questionable. Eight patients (Cases 1 through 8) had severe paralysis starting on the third to ninth day of the disease and had a corresponding lowering of the serum-potassium, which returned to normal on the administration of Darrow's solution or oral potassium chloride, given in the form of a syrup (one dram, equalling one gram of potassium chloride) three to four times a day. There did not appear to be any clinical improvement from the oral potassium chloride, although fair therapeutic trials were given. Darrow's solution was given to patients 1, 2, 3, 5, and 6, and seemed to be of questionable benefit, although a fair evaluation could not be made in so few patients. Four of these patients (Cases 1, 2, 3, and 6) had severe bulbar involvement.

TABLE I. SERUM POTASSIUM AND SODIUM IN POLIOMYELITIS*

| CASE NO. | NAME | AGE (YR.) | RACE, SEX | DAY OF DISEASE | SERUM POTASSIUM (MEQ./LITER) | SERUM SODIUM (MEQ./LITER) | CONDITION ON ADMISSION | CONDITION ON DISCHARGE |
|---|---|---|---|---|---|---|---|---|
| 1 | I. T. | 10 | N, f | 12 | 6.4 | | Rigidity of neck and back | No paralysis or weakness |
| | | | | 18 | 6.8 | 135* | | |
| 2 | C. A. W. | 11 | W, m | 9 | 4.48 | 161 | Weakness of both hips | No paralysis or weakness |
| 3 | D. J. | 2 | N, m | 8 | 5.2 | 145 | Weakness of both lower extremities | No paralysis or weakness |
| 4 | J. D. | 6 | W, m | 8 | 4.2* | | Weakness of all extremities | No paralysis or weakness |
| | | | | 10 | 5.75* | | | |
| 5 | M. G. | 17 | W, m | 6 | 4.59 | 154 | Spasm of back | No paralysis or weakness |
| 6 | L. H. | 10 | W, f | 4 | 4.7 | 147 | Spasm of back | No paralysis or weakness |
| 7 | R. M. | 1 | W, m | 4 | 5.41 | 104 | Spasm and rigidity of back | No paralysis or weakness |
| | | | | 13 | 4.1 | 136 | | |
| 8 | D. M. | 3 | W, f | 2 | 4.6 | 150 | Weakness of left leg | No paralysis or weakness |
| 9 | M. M. | 7 | N, f | 9 | 4.95 | 143 | Weakness of both legs | No paralysis or weakness |
| | | | | 16 | 4.3* | | | |

*Denotes chemical determination, all others were done by a flame photometer.

The results of seven determinations of spinal-fluid potassium on six patients with some paralysis, as well as a corresponding serum potassium, are shown in Table IV. The serum and spinal-fluid potassium were within normal limits and the spinal-fluid sodium was low in one (Case 2) and high in one (Case 4).

## DISCUSSION

Peters and Van Slyke[14] and Fenn[15] have shown that during increased muscular activity and metabolism there is a transfer of potassium from muscle cells into blood plasma, and during rest or anesthesia, a transfer from plasma back into the muscle cells, or that some of this potassium may be stored in the liver and later excreted in the urine. The muscles of suckling mice paralyzed by poliomyelitis virus lose potassium.[16] Darrow,[6] in an analysis of babies dying of diarrhea,

found a 40 per cent reduction in muscle potassium. It has previously been pointed out that low levels of serum potassium can result from (1) dilution of body fluids, (2) excretion in urine and other body fluids, (3) transfer from plasma into muscle cells, and (4) as result of low intake of potassium.[17]

In the cases presented here, there was no history of vomiting or diarrhea and the low potassium is possibly a result of a low intake, especially in the cases with severe paralysis and bulbar involvement, since these patients were unable to eat an adequate diet. Urinary potassium determinations were not made.

TABLE II. SERUM POTASSIUM AND SODIUM IN POLIOMYELITIS*

| CASE NO. | NAME | AGE (YR.) | RACE, SEX | DAY OF DISEASE | SERUM POTASSIUM (MEQ./LITER) | SERUM SODIUM (MEQ./LITER) | CONDITION ON ADMISSION | CONDITION ON DISCHARGE |
|---|---|---|---|---|---|---|---|---|
| 1 | B. L. | 17 | W, m | 10 | 4.22 | 160 | No weakness, bulbar | Scattered weakness of all extremities |
| | | | | 19 | 4.32 | 142 | | |
| 2 | R. S. | 17 | W, m | 2 | 4.48 | 142 | Bulbar, rapidly progressive | Died—4th day |
| | | | | 3 | 4.04* | | | |
| 3 | B. C. | 11 | W, m | 15 | 4.6 | 137 | Weakness of both hips | Scattered weakness of both legs |
| | | | | 16 | 4.48* | | | |
| 4 | C. C. | 16 | W, m | 3 | 4.18 | 140 | Weakness of both hips | Scattered weakness of both legs |
| | | | | 7 | 5.86 | | | |
| 5 | M. W. | 4 | N, m | 8 | 5.25* | | Weakness of all extremities | Scattered weakness of all extremities |
| | | | | 16 | 4.25 | 132 | | |
| | | | | 22 | 4.92 | 148 | | |
| 6 | A. G. | 19 | W, m | 7 | 4.11 | 145 | Weakness of upper extremities | Paralysis of left shoulder |
| | | | | 10 | 5.08 | 148 | | |
| 7 | C. C. | 16 | W, m | 12 | 4.1* | | Weakness of extremities, difficulty swallowing | Scattered weakness of left hip and leg |
| | | | | 18 | 5.85 | 162 | | |
| 8 | B. C. | 11 | W, m | 13 | 4.48 | 138 | Weakness of both hips | Scattered weakness of both legs |
| | | | | 16 | 4.48* | | | |
| 9 | E. W. | 3 | W, f | 15 | 4.85 | 138 | Weakness of all extremities | Scattered weakness of all extremities |
| | | | | 22 | 5.48 | 144 | | |
| | | | | 32 | 5.05 | 135 | | |

*Denotes chemical determinations, all others were done by a flame photometer.

Danowski[17] pointed out that there is only a limited variation of the potassium level in extracellular fluid under ordinary conditions; and this level can be raised to normal by the oral ingestion of potassium chloride.[18] The excess may be eliminated through the kidneys or may enter liver cells temporarily and later be excreted, the excretion taking place by glomerular filtration or through renal tubules.[19, 20] It has also been pointed out that a single dose of potassium chloride produced a transient rise in serum potassium followed later by muscle improvement.[21] Since the patients shown in Table III had low serum potassium levels, oral potassium chloride was tried, and on this therapy the serum potassium returned to normal; but no improvement was noted in the paralysis at any time which could be attributed to the potassium-chloride therapy. Due to the small number of cases and the short period of therapy, no definite conclusions can be drawn.

TABLE III. SERUM POTASSUM AND SODIUM LEVELS IN POLIOMYELITIS*

| CASE NO. | NAME | AGE (YR.) | RACE, SEX | DAYS 0-3 | 4-7 | 8-11 | 12-15 | 16-19 | 20-40 | | THERAPY | CONDITION ON ADMISSION | CONDITION ON DISCHARGE |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | B. E. | 11 | W, m | | (K) 3 (Na) 149 | 3.7 150 | | | 3.95 132 | 4.31 148 | Darrow's, plasma, and KCl | Weakness of lower extremities with bulbar symptoms | Weakness of lower extremities, improving |
| 2 | W. H. | 5 | W, f | | | | 3.35 147 | | 4.1 158 | 5.6 141 | Darrow's, KCl | Bulbar-respiratory type with paralysis left arm and right leg | Weakness legs, paralysis arms, died—88th day |
| 3 | E. S. | 5 | W, m | | 3.28 140 | 4.19 137 | | | 4.5 154 | | Darrow's and plasma | Bulbar-respiratory type with weakness upper extremities | Paralysis left arm and weakness right arm |
| 4 | N. L. | 13 | W, m | | 3.55 140 | | | 3.6 | 4.28 170 | | None | Weakness lower extremities | Paralysis both lower extremities |
| 5 | E. B. | 24 | W, f | | 3.78 130 | | 4.82 146 | | | | Darrow's and KCl | Weakness all extremities | Scattered weakness all extremities |
| 6 | M. M. | 21 | W, f | | 2.9 142 | 3.9 118 | 4.53 140 | | | 4.34 137 | Darrow's and KCl | Bulbar-respiratory type with weakness all extremities | Paralysis lower extremities, weakness upper extremities |
| 7 | B. C. | 16 | W, m | 4.98 137 | 3.2 | | 3.9 114 | 4.2* | | | KCl | Weakness left leg | Weakness left hip and leg |
| 8 | A. H. | 5 | N, m | | | | 3.7 142 | | 4.2* | | KCl | Weakness both lower legs | Severe scattered paralysis all extremities |
| 9 | D. T. | 7 | N, f | | 3.65 125 | | 4.1 148 | | | | KCl | Marked nuchal rigidity | No paralysis or weakness, muscles good |
| 10 | P. F. | 10 | W, f | | | 3.6 136 | 4.2* | | | | KCl | Rigidity of back | No paralysis or weakness |

*Denotes chemical determinations, all others were done by a flame photometer. K=serum potassium (meq./liter). Na=serum sodium (meq./liter). Darrow's=Darrow's sodium lactate, potassium, and sodium chloride solution. KCl=potassium chloride syrup.

TABLE IV. BLOOD AND SPINAL FLUID SODIUM AND POTASSIUM IN POLIOMYELITIS*

| CASE NO. | NAME | AGE (YR.) | RACE, SEX | DAY OF DISEASE | BLOOD | | SPINAL FLUID | | CONDITION ON ADMISSION | CONDITION ON DISCHARGE |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | K | Na | K | Na | | |
| 1 | M. M. | 21 | W, f | 6 | 3.9 | 118 | 2.9 | 155 | Difficulty swallowing, weakness lower extremities | Paralysis lower extremities, weakness upper extremities |
| 2 | J. C. | 11 | N, f | 5 | 4.1 | 143 | 2.2 | 117 | Weakness extremities, difficulty swallowing | Weakness trunk and both upper extremities |
| 3 | C. C. | 16 | W, m | 3 | 4.18 | 140 | 2.45 | 141 | Weakness of hips | Paralysis left hip and leg—weakness of right hip and leg |
| 4 | J. W. | 8 | N, m | 5<br>9 | 4.52<br>4.25 | 142<br>142 | 3.<br>2.95 | 175<br>143 | Paralysis both upper extremities | Paralysis both upper extremities, bulbar, died—96th day |
| 5 | E. W. | 3 | W, f | 15 | 4.85 | 138 | 2.98 | 149 | Weakness all extremities | Scattered paralysis all extremities |
| 6 | L. S. | 12 | W, f | 8 | 4.62 | 141 | 2.6 | 151 | Weakness right arm, left leg | Weakness left leg |

*K=potassium (meq./liter). Na=sodium (meq./liter).

SUMMARY

1. Serum sodium and serum potassium determinations were carried out on fifty-six patients with poliomyelitis. Results of thirty-two cases are presented here.

2. There did not appear to be any correlation between the serum-potassium level and the severity of the paralysis.

3. Low serum-potassium levels were found in ten patients with severe paralysis or with bulbar involvement.

4. Oral potassium chloride did not appear to cause any improvement in the paralysis; however, no definite conclusions can be drawn as there were too few patients. Further studies are possibly warranted in cases with low potassium levels.

The author is greatly indebted to the Departments of Biochemistry and Clinical Pathology for carrying out the determinations.

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# A SIMPLE, SAFE BRONCHOGRAPHIC TECHNIQUE FOR CHILDREN

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BRONCHOGRAPHY is performed in far fewer cases than is desirable. The chief reasons are the technical difficulties for the operator, and the discomfort and danger to the patient. In children, both of these factors are greatly magnified.

Most physicians tend to avoid bronchography in children. Many resort to bronchoscopy or tracheal catheterization for the instillation of Lipiodol; some perform the procedures under general anesthesia.[1] The risks and unpleasant consequences of these procedures are factors which the physician hesitates to impose for a diagnostic test.

In adults and older children, many attempts have been made to avoid such drastic measures by abolishing the cough, gag, and swallowing reflexes with a surface anesthetic, and allowing the Lipiodol to flow from the pharynx into the bronchial tree by gravity.[2] In practice, however, this is often very difficult. The use of atomization, swabbing, and laryngeal or tracheal cannulation to obtain anesthesia may cause such violent gagging, swallowing, and coughing as to result in complete loss of patient cooperation and make the procedure impossible to perform. This is particularly true in children. In addition, these techniques usually utilize far more than toxic amounts of the anesthetic agent,[3] and deaths have been reported from their use.[4]

A third factor discouraging bronchography in private practice is the expense of a procedure requiring the concomitant services of a radiologist, laryngologist, and possibly an anesthetist. All these factors tend to limit its performance to the group-clinics and hospitals of larger cities. There is great need for a procedure that is simple to perform, relatively free of discomfort or danger to the patient, and easily adaptable to office use.

In attempting to simplify bronchography and decrease its difficulties in children, a new technique has been evolved which is advantageous for adults as well. It is based primarily on nebulization of the surface anesthetic, as described in previous reports.[5, 6] As originally employed, this procedure required about thirty minutes for anesthesia. We have succeeded in reducing the time to twenty minutes and further improving the anesthesia for bronchography and bronchoscopy by adding to the anesthetic solution a detergent (Triton A-20)§ for its spreading and penetrating properties, and a droplet stabilizer (glycerin) to inhibit evaporation of the small droplets before they are deposited in the respiratory passage. Epinephrine is added for its vasoconstricting effect to de-

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‡Former Resident in Radiology, Sea View Hospital.
§Supplied by Röhn & Haas Co., Inc., Philadelphia.

lay absorption of the anesthetic drug. For the anesthetic drug, we employ 0.5 per cent pontocaine, which confers an anesthesia of thirty minutes' duration. Cocaine is not employed because of its toxicity.

Another factor in shortening the time required is the rate of oxygen flow. Whereas we originally used a rate of 6 liters per minute for thirty minutes, we now increase the rate to 10 to 12 liters per minute once the preliminary anesthesia of the pharynx has been obtained. Thus the same amount of solution is nebulized in a shorter period of time.

## OUTLINE OF PROCEDURE

*Materials (Fig. 1).—*

1. DeVilbiss #40 nebulizer with rubber stopper in side vent, and with rubber mouthpiece 3 inches long and ½ inch in diameter attached to oral end of nebulizer.
2. Oxygen tank and gauge, with gum-rubber tubing connecting gauge to nebulizer.
3. Anesthetic solution (described above).
4. Adhesive tape, one inch wide, for occluding nostrils.
5. Gauze squares for holding tongue forward.
6. Forty per cent Lipiodol, 20 c.c. vial.
7. Syringe, 20 c.c., with a 3-inch length of fine catheter tubing attached.
8. Tilt stretcher or tilt x-ray table.

*Preoperative Orders (dosages appropriate for age).—*

1. Postural drainage on arising (if secretions are copious).
2. No breakfast and nothing by mouth.
3. Nembutal, two hours before bronchography.
4. Morphine or codeine sulphate } (one-half hour before bronchography).
5. Atrophine sulphate }
6. Postural drainage on return to ward or home, 30 minutes, once.
7. No food or fluids until ½ hour after bronchography.

*Technique of Anesthesia (Fig. 2).—*

1. Introduce 8 c.c. of anesthetic solution into the nebulizer and close the side vent with the rubber stopper.
2. Tape off the nostrils so that the patient must breathe through the mouth, and have him pull the tongue forward with a gauze square. Demonstrate the mist to the patient and have him hold the rubber mouthpiece of the nebulizer in his mouth and inhale the mist.
3. Use an oxygen flow of 6 liters per minute for the first 5 minutes while the patient inhales the mist; then continue at 10 liters per minute for a total of 20 minutes.
4. During nebulization have the patient change the direction of the mouthpiece in such a way that he obtains a direct impact on the lateral walls of the pharynx as well as in the midline, and have him gradually advance the mouthpiece deeper into the pharynx as the anesthesia progresses.
5. Remove the adhesive tape from the nostrils, and have the patient disrobe to the waist in preparation for x-ray.

*Technique of Lipiodol Administration (Fig. 3).—*

1. Have the patient lie on the tilt stretcher under the x-ray tube, with his feet at the adjustable end so that they can be elevated at the proper time. With

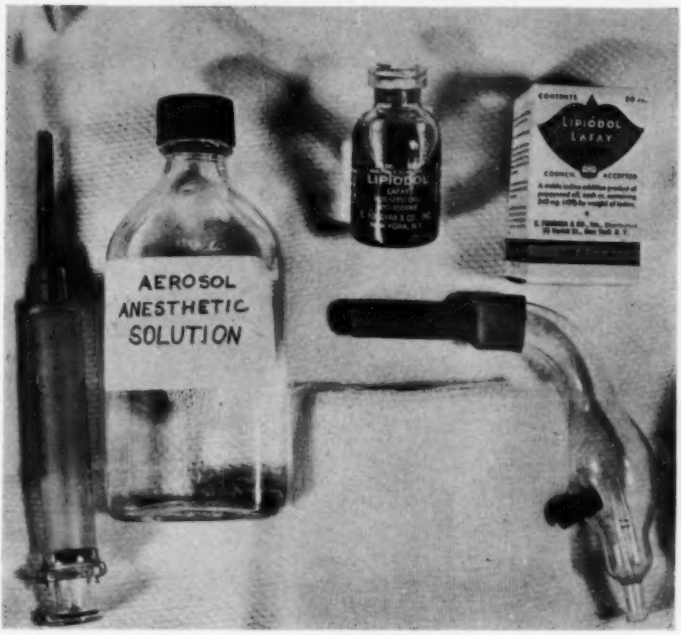


Fig. 1.—Materials employed. Note that the only instruments required are a nebulizer and a syringe. No endoscopic instruments are needed.

Fig. 2.—Technique of aerosol anesthesia. The child simply inhales the mist produced by the nebulizer. A complete surface anesthesia of the respiratory mucosa is thus obtained without discomfort to the patient or difficulty to the physician.

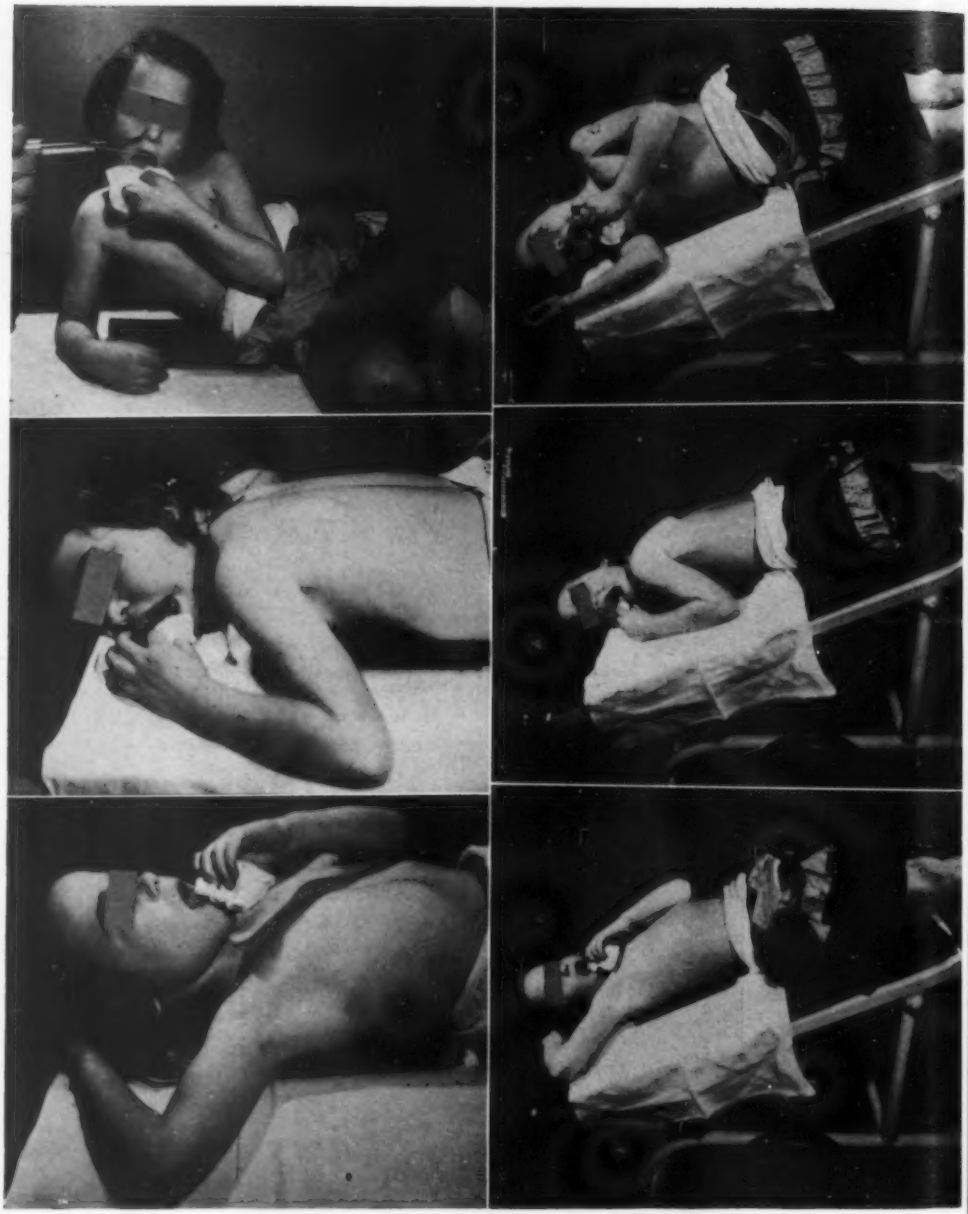


Fig. 3.—The administration of Lipiodol, and the positioning procedure employed. The first position (*A*) is maintained for 60 seconds to allow the Lipiodol to pass the larynx. All other positions are maintained for 20 seconds each. Note the simplicity of the positions, the last three positions being duplicates of the first three except that the head is lowered.

the table horizontal, the patient lies on the side to be studied bronchographically, supporting himself on his elbow so that his body is in the lateral position and at an angle of about 30 degrees from the horizontal.

2. To prevent loss of time later, place the x-ray cassette under the patient and label it before the Lipiodol is instilled.

3. Have the patient hold his tongue completely forward with gauze, and instruct him not to release it until just before the x-ray film is to be exposed. Caution him not to cough or swallow. If the patient is a young child, have an assistant hold the tongue.

4. Insert the catheter tip of the Lipiodol syringe 2 or 3 inches into the nostril, being careful not to reach the esophagus, and inject the Lipiodol rapidly into the nasopharynx.

a. The injection takes about 45 seconds, and the Lipiodol gurgles for an additional few seconds as it passes through the larynx.

b. Now there is a continuous column of Lipiodol extending from the larynx to the lower lobe; that stream will be diverted by positioning so as to enter the various branches of the bronchial tree.

Fig. 4.—Postural drainage. This is begun immediately after exposure of the x-ray films, so that the Lipiodol is evacuated before it is able to flow into the alveoli.

5. Within 60 seconds after beginning the injection, the catheter is removed and the patient is turned to the prone position for 20 seconds, then to the supine position for 20 seconds. This fills the lower lobe and the middle lobe or lingula.

6. The foot end of the stretcher is immediately elevated to about 45 degrees and the patient positioned laterally, anteriorly, and posteriorly for 20 seconds each. This fills the entire upper lobe.

7. The x-ray films are then exposed. They are, in order:

a. Lateral

b. Postero-anterior

8. Postural drainage is begun immediately (Fig. 4) with forced tussive squeezing for 30 minutes (no coughing). This usually eliminates the Lipiodol from the trachea and the lower and middle lobes.

9. The patient is returned to the ward or home, ambulatory, so that the Lipiodol in the upper lobe drains downward. On arrival he repeats the postural drainage once for 30 minutes.

*Precautions.—*

1. The anesthesia cannot be hurried. If aerosol is administered less than 20 minutes, an occasional failure may occur.

2. The timing of the positioning is important. The total positioning time is at least 3 minutes, yet no more than about 4 minutes may elapse between the beginning of injection of Lipiodol and the exposure of the x-ray films, in order to prevent alveolar deposition.

3. The viscosity of unheated 40 per cent Lipiodol is perfect for this technique; 28 per cent Iodochloral and other oils of low viscosity run into the alveoli too quickly and do not allow time for positioning.

## DISCUSSION

A great value of this technique is its lack of discomfort to the patient. As already discussed, conventional methods of obtaining surface anesthesia involve atomization, swabbing, and laryngeal or tracheal instillation, all of which result in repeated gagging, swallowing, and coughing. Aerosol anesthesia is free of such unpleasant consequences; the patient simply sits quietly and inhales the mist. The anesthesia is complete and widespread throughout the respiratory passages. Due to the excellence of the anesthesia, there is no need to catheterize the trachea for injection of Lipiodol; the absence of the cough, gag, and swallowing reflexes allows the Lipiodol to pass down easily from the nasopharynx, sparing the patient the discomfort and annoyance of endotracheal instrumentation. The universal willingness of the patients to return a few days later for bronchography of the other lung is an indication of its lack of discomfort.

A second value of the procedure is its simplicity. It requires no fluoroscope and no endoscopic instruments, nor any skill in using them. The positioning is free of the complicated maneuvers often associated with bronchography.

The third value of this technique is its relative safety. All major procedures and traumatic manipulations are avoided. The amount of anesthetic agent used is far below toxic levels, in contrast to other techniques which often utilize several times the toxic dose. When aerosols are produced continuously in the manner described, only 15 per cent of the solution is actually retained by the patient.[6-10] Thus the amount absorbed in this procedure is approximately 1.20 c.c. of 0.5 per cent pontocaine. The widespread anesthesia is accomplished with this relatively minute amount of material because of the great number and extremely small size of the aerosol particles. As these particles settle on the mucosa of the upper respiratory tract, the detergent makes them tend to spread out and form a continuous film. The possibility of swallowing the anesthetic agent, with rapid gastric absorption and toxic blood levels, is diminished by the absence of pools of the solution in the pharynx and the absence of any stimulation to gag and swallow.

One type of patient particularly difficult to anesthetize is the type with chronic suppurative disease with thick purulent bronchial secretions. The addi-

tion of the detergent to the solution decreases the difficulty in that it tends to liquify the sputum and allow better penetration by the anesthetic agent.

Another desirable feature is the rapid elimination of Lipiodol from the tracheobronchial tree by prompt drainage. This tends to prevent side-reaction from the iodized oil itself, removes a major objection to bronchography in the presence of tuberculosis, and keeps the lung fields from being obscured for months by alveolar deposition.

A time-saving aspect of the technique is that, when several patients must be handled consecutively, each can be anesthetizing himself under supervision while the preceding patient is being bronchographed. Thus, many bronchograms can be performed in a single morning, instead of the customary one or two.

The technique described fulfills the requirements of ease, simplicity, safety, and comfort. It is relatively inexpensive because it can be performed by a single physician without highly specialized instruments or training. While bronchography in children may never be as simple to perform as a blood count, there is little need to avoid it or to fear its consequences when this technique is employed.

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# GENERALIZED HISTOPLASMOSIS IN INFANTS AND CHILDREN

## Review of Ten Cases, One With Apparent Recovery

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THE purpose of this paper is to report briefly on the occurrence of generalized histoplasmosis in an infant with recovery, and the manifestations of generalized histoplasmosis in nine children who died of the disease.

Since first described by Samuel T. Darling[1] in 1906, histoplasmosis seems definitely to be increasing in incidence. This is apparent in the increasing numbers of case reports which have been published since 1939 especially. The first case recognized in St. Louis Children's Hospital was by autopsy in 1942.[16] Since that time we have seen a total of ten cases of generalized histoplasmosis, and one case of localized histoplasmosis in a cervical lymph node of an infant who died from Hand-Christian-Schüller's disease. In reviewing autopsies since 1918 performed for the St. Louis Children's Hospital by the Department of Pathology, Washington University School of Medicine, Dr. Margaret Smith[2] has been unable to find a case in the pediatric age group prior to 1942. Parsons and Zarafonetis[3] also state that in a review of thousands of autopsies, no overlooked cases were found. In its fatal, generalized form it is still a relatively unusual disease, but one that must be thought of more frequently as the typical signs and symptoms are manifested.

The literature on histoplasmosis and its manifestations has been well summarized and presented elsewhere[3-6] and will not be further elaborated on here. Smith[7] probably first suggested that many people in the Central United States who had multiple areas of calcification in chest films, and who were both tuberculin and coccidioidin skin-test negative, might be examples of healed histoplasmosis. Since then numerous papers have been written to show that in the Eastern Central United States there is a high percentage of people with positive skin tests to histoplasmin who are negative to tuberculin tests.[8-11] Such a review received support recently when Bunnell and Furcolow[12] reported two cases of generalized histoplasmosis with recovery and one in which recovery seems probable. An additional case, an infant who recovered, has been reported by Blumberg, Ruehman, and Johansmann.[13]

### PROTOCOL OF INFANT WHO RECOVERED

J. K. H., a 19-month-old white female infant, was first admitted to St. Louis Children's Hospital on Jan. 13, 1949.* She was born on May 22, 1947, one of identical twins, birth weight 3 pounds, 6 ounces. Her mother had intermittent vaginal bleeding from the fifth to ninth month of gestation although otherwise she had been well. At birth the patient had considerable difficulty because of aspiration of amniotic fluid, but did fairly well and was discharged from the hospital at 3 months of age. She did well then until the onset of the present illness except for chicken pox in September, 1948, and a few mild respiratory infections.

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*I wish to acknowledge my indebtedness to Dr. J. C. Jaudon, whose patient this was, for allowing me to follow her recovery.

In mid-November, 1948, the older sisters of the patient developed typical pertussis. On Dec. 1, 1948, the patient developed a paroxysmal cough, with whoop and vomiting, diagnosed as pertussis. The symptoms were not too severe, but on December 19 she suddenly became acutely ill with chills, fever, sweating, and grunting respirations. She received penicillin but gradually got worse, so that by December 24 she required hospitalization at another hospital. There she received penicillin, streptomycin, and oxygen, but became comatose. She developed swelling of the ankles and legs and it was thought she was not going to live. However, after several days she gradually began to improve. She was sent home on Jan. 6, 1949, only to have symptoms of cough and grunting respirations recur several days later. She was then admitted to St. Louis Children's Hospital on Jan. 13, 1949.

The family history was interesting in that the identical twin of the patient developed symptoms of pertussis concurrently with the patient, and had to be hospitalized also. She developed convulsions shortly after admission and expired. Autopsy was not done. Six other siblings seemed well as did the parents. None of the family's domestic animals appeared ill.

On entry, the patient seemed both acutely and chronically ill. Temperature was 38.6° C., respirations 72, and pulse 142. She had signs of pneumonia involving the entire right upper lobe and of scattered areas of bronchopneumonia throughout the rest of the lungs. The abdomen was distended; the liver was felt 4 cm., and the spleen 6 cm. from the costal margins. A chest film obtained on Jan. 14, 1949, confirmed the physical findings of right-upper-lobe pneumonia and generalized bronchopneumonia (Fig. 1). She received penicillin and streptomycin for twelve days and after the third day remained afebrile. Myocardial decompensation developed the second hospital day but recovery with digitoxin therapy was prompt. Improvement in the lung findings was slow, despite the rapid general improvement.

Laboratory data at the time of admission was as follows: hemoglobin 6.4 Gm. per cent; red blood count 3.3 million; white blood count 18,950. The differential showed basophiles 1, eosinophiles 5, stab cells 19, segmented 20, lymphocytes 57. A few nucleated red blood cells were seen on smear, and platelets were plentiful. Tuberculin and histoplasmin skin tests were negative. Because of the hepatosplenomegaly, anemia, and chest findings, a bone marrow aspiration was done on Jan. 18, 1949 (fifth hospital day), and cultures on Sabouraud's media were made. The marrow smears were normal hematologically, and careful search, including concentrated smears, did not reveal any *Histoplasma capsulatum* organisms. However, after three weeks' time a growth occurred on Sabouraud's media which was identified as typical *H. capsulatum* by Dr. Parker Beamer of the Department of Pathology, Washington University School of Medicine.

By this time the patient was clinically well and had been discharged from the hospital on February 9. At the time of discharge the lungs were still hazy on fluoroscopy, the hepatosplenomegaly was only slightly less, and the peripheral white blood count was 5,300 with a shift similar to that on admission.

The patient was readmitted to the hospital for re-evaluation on March 14, 1949, at which time she was asymptomatic although she had had an episode of "pneumonia" at home in February. She was afebrile, had a normal blood hemogram, the liver was palpable 3 cm. and the spleen 3 cm. below the costal margin, both being much smaller. Her histoplasmin skin test was again negative on March 16 and March 28. Bone marrow cultures on Sabouraud's media on March 15 and 24, were negative. On April 8, 1949 (four months after onset of pertussis-like illness), the histoplasmin skin test was strongly positive with an 8 mm. area of induration and a 2 cm. area of erythema. As can be seen in Fig. 2 the chest film taken March 15, 1949 (three months from onset), still showed bronchopneumonic-type infiltration.

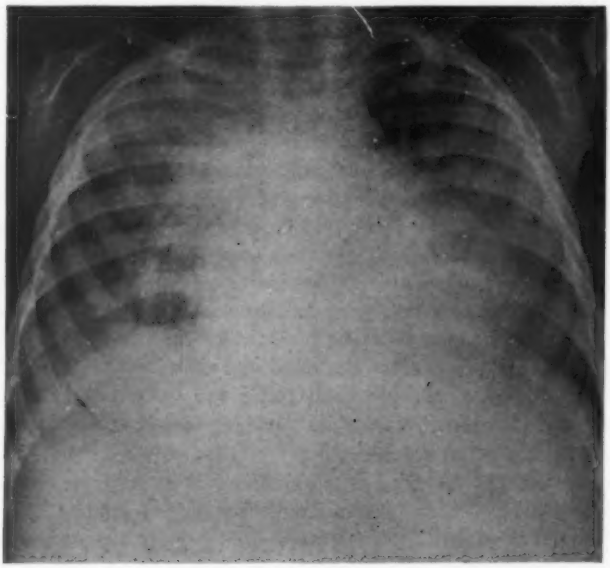

Fig. 1.—Chest film of J. K. H. one month after onset of symptoms and when patient was acutely ill showing extensive bronchopneumonia bilaterally and lobar involvement of the right upper lobe.

On April 7, 1949, blood serum was tested for complement fixation* to *H. capsulatum* and was reported by Dr. Furcolow as "very suspicious of active histoplasmosis." This was repeated on June 8, and reported as showing "slightly less fixation than previously but still to be classed as 'suspicious.'" On April 23, 1949, she was skin-tested as follows:

| *0.1 c.c. intracutaneously* | | *Results: 48 hours* |
|---|---|---|
| Blastomycin | 1/1,000 | Negative |
| Coccidioidin | 1/100 | Negative |
| Histoplasma | 1/1,000 | Strongly positive (1 cm. wheal) (2 cm. erythema) |

*Through the kindness of Dr. M. L. Furcolow, United States Public Health Service, Kansas City, Kan.

Further follow-up has shown her to remain afebrile and asymptomatic for twelve months after the onset of her illness. She has gained weight and grown normally both physically and mentally. The liver is normal in size, the spleen tip is still palpable, and the hemogram remains normal. A chest film on June 8, 1949 (Fig. 3), and also August 10, showed clearing of the parenchyma with definite right hilar glandular enlargement, but no calcification was visible.

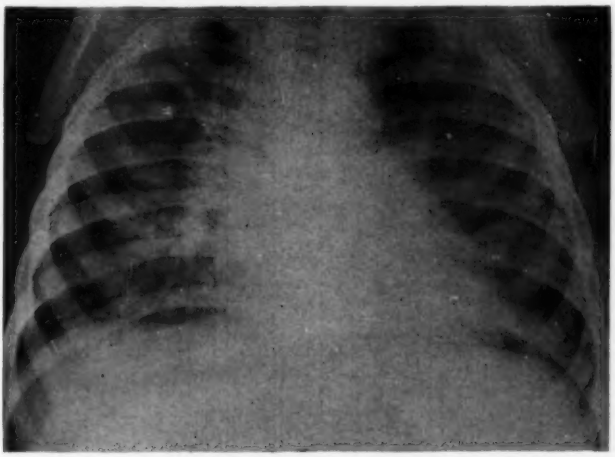

Fig. 2.—Chest film of J. K. H. three months after onset showing clearing, but still extensive involvement when patient was clinically well.

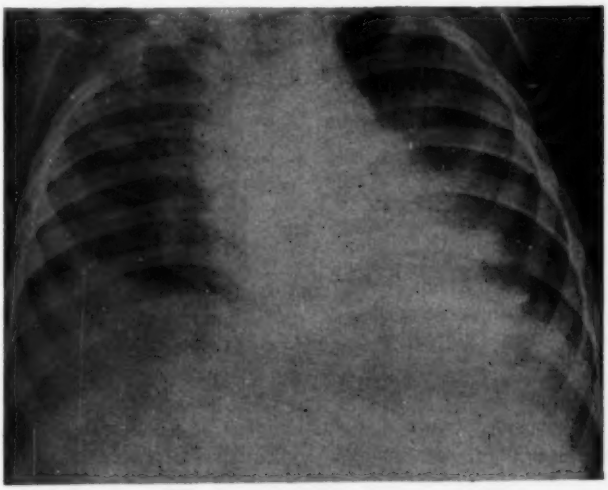

Fig. 3.—Chest film of J. K. H. six months after onset showing almost complete clearing and no evidence yet of pulmonary calcification.

On Aug. 10, 1949, the blood serum showed minimal complement fixation. Dr. Furcolow has found that the complement fixation test has become less positive as the patients recovered.

TABLE

| NAME, RACE, SEX | AGE | ADMISSION — DEATH | FAMILY HISTORY | FEVER | ANOREXIA | WEAKNESS | COUGH | FURUNCLES | SPLENOMEGALY | HEPATOMEGALY | PETECHIAE | GLAND ENLARGEMENT | BRONCHO-PNEUMONIA |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| J. D. J.<br>W ♂ | 11 mo. | 6-26-42<br>6-27-42 | Negative | + | + | + | + | + | + | + | + | | + |
| S. M. B.<br>W ♀ | 4 yr.,<br>2 mo. | 3-22-43<br>3-26-43 | Siblings O.K. | + | + | + | + | + | ++ | ++ | | + | + |
| S. J. N.<br>W ♂ | 14 mo. | 2- 4-44<br>2- 4-44 | Negative | + | + | + | + | | ++ | ++ | ++ | | |
| J. A. M.<br>W ♀ | 2 yr.,<br>10 mo. | 1-24-47<br>1-30-47 | Negative | + | + | + | + | | | + | + | + | + |
| S. K. D.<br>W ♀ | 3 yr.,<br>8 mo. | 7- 9-47<br>8-21-47 | Mother: skin test positive | + | + | + | + | + | +++ | ++ | | + | + |
| D. Y. T.<br>N ♀ | 4½ mo. | 8-30-47<br>9- 6-47 | Negative | + | + | + | + | + | +++ | +++ | | | + |
| C. L. B.<br>W ♀ | 6 mo. | 9-30-47<br>11-17-47 | Mother and father: skin test positive | + | + | + | + | | ++++ | ++ | | | + |
| J. Q. Mc.<br>N ♂ | 9 mo. | 12- 3-47<br>12-11-47 | Negative | + | + | + | + | | ++++ | ++ | + | + | + |
| P. S. M.<br>W ♀ | 7 mo. | 11-11-48<br>12-22-48 | Twin died with same symptoms | + | + | + | + | | +++ | + | | | + |
| J. K. H.<br>W ♀ | 20 mo. | 1-13-49<br>Recovered | Twin died with same symptoms | + | + | + | + | | ++++ | +++ | | + | ++ |

The nine other cases of disseminated histoplasmosis which were fatal were seen as follows:

1942—1 diagnosed at autopsy
1943—1 diagnosed at autopsy
1944—1 diagnosed at autopsy
1947—5 diagnosed clinically (lymph node biopsy—1; bone marrow culture—4)
1948—1 diagnosed clinically (bone marrow culture)

No explanation is apparent for the large number of cases in 1947.

The nine cases are presented in summary form in Table I. There are pertinent remarks which should be made about some of them.

Practically all had early symptoms of lower-respiratory tract involvement and at some time in their course, and always terminally, developed physical signs of bronchopneumonia. There were no uniform findings in the chest films

I.

| LEUCOCYTOSIS | LEUCOPENIA | THROMBOPENIA | LEFT SHIFT | ANEMIA Hb GM. % | BLOOD CULTURE | BONE MARROW CULTURE | SKIN TEST | LYMPH NODE BIOPSY | AUTOPSY<br>WASHINGTON UNIVERSITY DEPARTMENT OF PATHOLOGY NUMBER |
|---|---|---|---|---|---|---|---|---|---|
| 16,100 | | | + | 6.7 | | | | | #9882 Histoplasmosis: lungs, liver, spleen, kidneys, lymph nodes of mediastinum, periaortic regions, and of mesentery of intestines. Acute ulcers of colon. |
| | 1,800 | + | + | 4.8 | | | | | #10440 Histoplasmosis: lungs, liver, spleen, skin, bone marrow, lymph nodes of thorax and abdomen. |
| | 3,550 | + | + | 7.0 | *E. coli* | | | | #11019 Histoplasmosis: lungs, liver, spleen, kidneys, testes, lymph nodes, bone marrow. |
| | 4,400 | − | + | 6.4 | | | | + | #12425 Histoplasmosis: cervical, axillary peritracheal, peripancreatic, periaortic, perihepatic, iliac, inguinal lymph nodes. Duodenum, jejunum, ileum, colon, rectum, adrenals. Ulcerative enteritis. |
| 18,100 | 3,050 | + | + | 6.0 | + | +<br>+<br>+ | −<br>−<br>−<br>− | + | None. |
| | 2,400 | + | + | 7.5 | − | + | − | | None. |
| | 1,000 | + | + | 9.6 | + | +<br>+ | −<br>−<br>− | | None. |
| 10,250 | 4,850 | + | + | 8.2 | + | + | −<br>− | | #12864 Histoplasmosis: lymph nodes, bone marrow, liver, spleen, intestines, lungs, kidneys, myocardium, middle ears. Foci of ulcer and necrosis ileum and colon. |
| | 4,200 | + | + | 4.7 | + | +<br>+<br>+ | −<br>− | | #13345 Histoplasmosis: lungs, liver, spleen, bone marrow, lymph nodes, ileum. Multiple ulcerations intestines. |
| 18,950 | 5,300 | − | + | 6.4 | | +<br>−<br>−<br>− | −<br>−<br>++ | | |

on these patients although several showed widespread patchy infiltrative lesions bilaterally, called either atypical pneumonia or bronchopneumonia. An example is seen in Fig. 4 which is the chest film taken on entry of S. M. B. All subjects examined post mortem showed *H. capsulatum* organisms both interstitially and contained in large macrophages in the alveolae. There was little evidence of polymorphonuclear infiltration. Figure 5 is a photomicrograph of the lung involvement. Most prominent is the large multinucleated macrophage which is packed with *H. capsulatum* organisms. On close examination one can see that there are mononuclear cells, also crowded with organisms, in the interstitial tissues.

The liver involvement is manifested by large areas of necrosis, irregular in pattern, and in such areas there is infiltration by the *H. capsulatum* organisms. Figure 6 is a photomicrograph of the edge of one of the necrotic areas. This

case also demonstrates the typical picture as seen in the lymph nodes (Fig. 7) where the sinusoids are crowded with the organisms. As an interesting microscopic finding, Fig. 8 shows a blood vessel in the spleen which contains numerous mononuclear cells loaded with the organisms. Figures 5 through 8 are representative of the generalized involvement in patient S. M. B.

J. A. M.'s was a most interesting case because of the widespread demonstrable lesions. She developed a paroxysmal cough in April, 1946, which was diagnosed as pertussis with pneumonia. She was hospitalized in Oklahoma and improved some on penicillin and streptomycin, but continued to have intermittent fever, listlessness, and sweating all summer. Two months before entry in January, 1947, more acute symptoms intervened so that she was again hos-

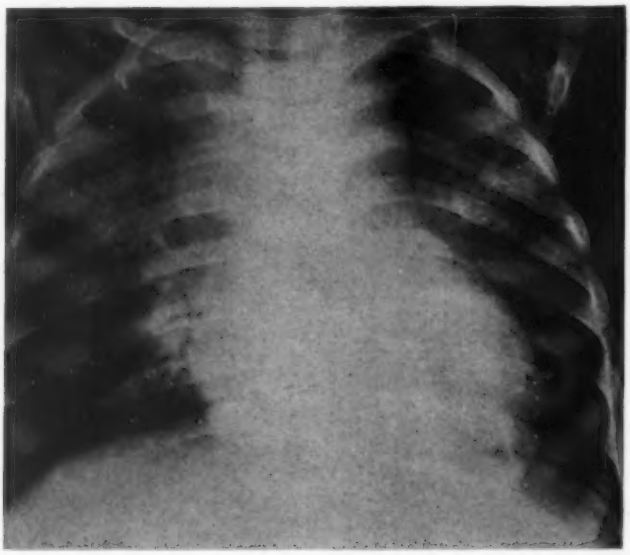

Fig. 4.—Chest film of S. M. B. Bilateral involvement suggestive of atypical pneumonia.

pitalized where she was found to have an anemia, leucopenia, and marked left shift to the Schilling differential. Despite blood transfusions she continued to be anemic. X-ray pictures of her bony skeleton were surprising and confusing. There were multiple areas of radiolucency of the skull (Fig. 9), scapulae, and femurs (Fig. 10). In the long bones (Fig. 10) there were marked periosteal reaction. The x-rays were interpreted as being due to a nutritional disturbance of bone which was healing, but such things as osteomyelitis and neuroblastoma with metastases were considered. A lymph node biopsy made the diagnosis with the finding of *H. capsulatum* organisms throughout the section. At autopsy the widespread lesions were easily demonstrable. Examination of the skull was not permitted. In Fig. 11 can be seen an ulceration of the colon extending to the muscle layer with granulomatous reaction in that area. Under higher power

there are numerous free *H. capsulatum* organisms as well as many contained in the mononuclear cells. The adrenal glands were extensively involved also. Figure 12 is a low power photomicrograph of an adrenal gland showing the

Fig. 5. Fig. 6.

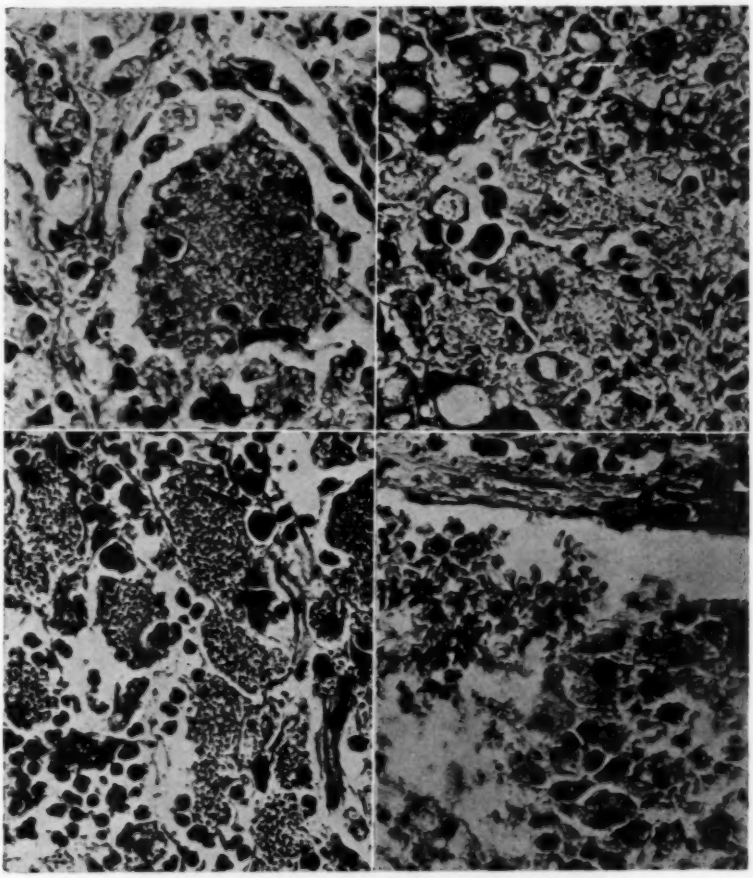

Fig. 7. Fig. 8.

Fig. 5.—Photomicrograph (high power) of lung (S. M. B.) showing large multinucleated macrophages in the center which is loaded with Histoplasma capsulata. Mononuclear cells containing the organism are scattered in the field.

Fig. 6.—Photomicrograph (high power) of liver (S. M. B.). Edge of a necrotic area infiltrated with *Histoplasma capsulata.*

Fig. 7.—Sinusoids of spleen (S. M. B.) crowded with *Histoplasma capsulata.*

Fig. 8.—Blood vessel in spleen (S. M. B.) containing numerous mononuclear cells loaded with *Histoplasma capsulata.*

granulomatous change with caseation and complete disruption of the normal architecture. Here, too, Histoplasma are easily found. In the bones the lesions were that of marrow hypoplasia of hemopoietic elements and large areas of

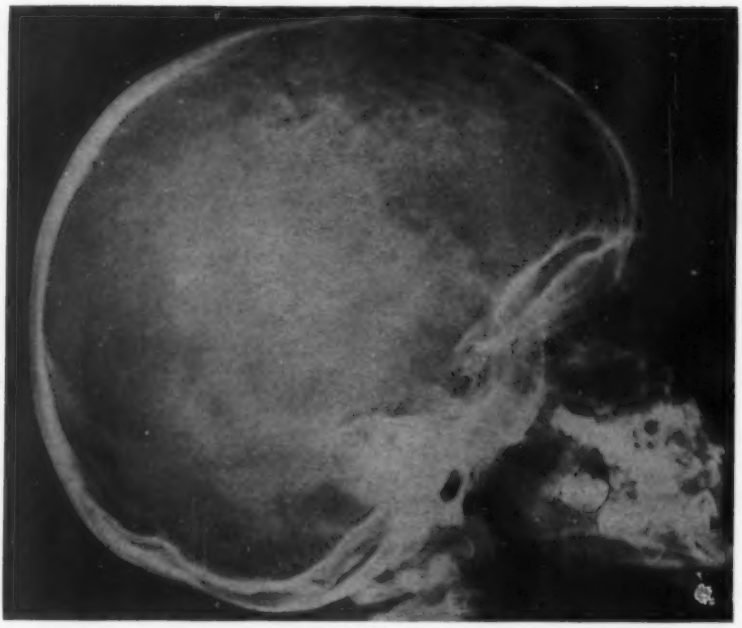

Fig. 9.—Multiple areas of radiolucency of skull in case of histoplasmosis (J. A. M.).

Fig. 10.—Radiolucent areas and marked periosteal reaction of femurs in case of histoplasmosis (J. A. M.).

granulomatous change (Fig. 13). Under oil immersion power in a granulomatous area of a clavicle the typical organisms are easily seen in large macrophages (Fig. 14). The radiographic findings as described here have not been described before in the literature.

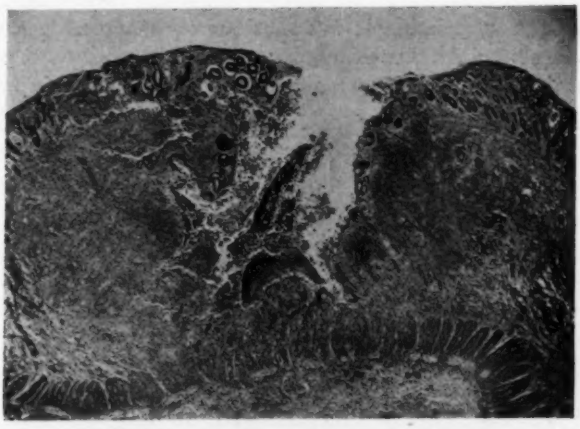

Fig. 11.—Ulceration of colon (J. A. M.) due to histoplasmosis. (Lower power.)

C. L. B. showed rather typical symptoms and physical findings of histoplasmosis with confirmation by bone marrow culture of the organism. She was skin tested with other materials to see if any cross reaction would occur. The results of the tests* were as follows:

| *0.1 c.c. intracutaneously* | *Result: 48 hours* |
|---|---|
| Histoplasmin (mycelial forms) | Negative |
| Coccidioidin | Negative |
| Blastomycin | Negative |
| Histoplasmin (killed yeast forms) | Negative |

P. S. M. was admitted with the history of a respiratory infection of five weeks' duration which had become worse and had not responded to adequate dosage of penicillin, streptomycin, and sulfonamides. On physical examination she was pale, there was hepatosplenomegaly but no obvious signs of infection other than a temperature of 40.2° C. The laboratory data were as follows: hemoglobin 4.7 Gm. per cent; red blood count 2.96 million; white blood count 4,200; hematocrit 18.2. Red blood count indices were MCV = 61.5 cu. $\mu$; MCH = 15.9 $\gamma\gamma$; MCHC = 25.8 per cent which were microcytic hypochromic indices. A Schilling differential of peripheral blood was stab 2, segmented 10, lymphocytes 88, platelets 20,000. Reticulocytes 2.0 per cent. Bone marrow examination was done on Nov. 12, 1948, which showed the typical picture of megaloblastic anemia in that all of the red blood cell precursor elements were atypical cells, i.e., megaloblasts in various stages of unequal maturation and degeneration. No *H. capsulatum* organisms were seen, but a culture of the marrow grew out the organism

*Kindly supplied by Dr. N. F. Conant, Department of Bacteriology, Duke University School of Medicine.

in six days' time. In the meantime she was given folic acid 15 mg. per day with only a 9 per cent reticulocyte response in four days' time. This response probably was depressed some because of intervening blood transfusions. Repeat bone marrow examination seven days later on Nov. 19, 1948, showed completely normal appearing erythroid elements with actual erythroblastic hyperplasia. There was also a myeloid left shift and this was subsequently manifest in the peripheral blood by a left shift. At this examination many histoplasmin organisms were seen, contained intercellularly in mononuclear cells and large macrophages.

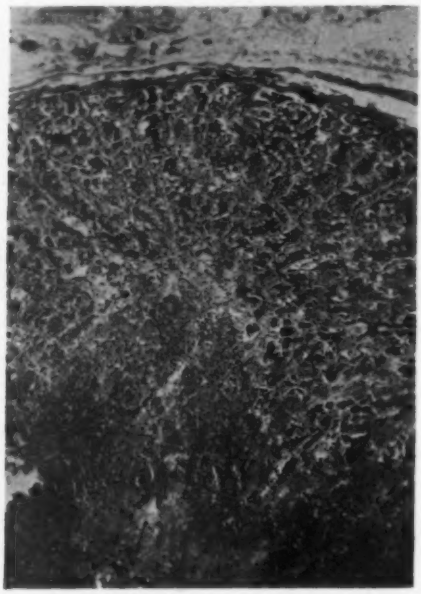

Fig. 12.—Adrenal glands (J. A. M.) showing granulomatous change with caseation in case of histoplasmosis. (Low power.)

In summary, it may be stated that clinical symptoms suggested those of nonspecific chronic respiratory disease. Many of the patients had initial diagnoses of pertussis because of the paroxysmal cough and whoop. However, they all had variable fever which is unusual in uncomplicated pertussis. Hepatomegaly was present in all patients, splenomegaly in all but one. In general the enlargement was marked. Four patients had petechiae and all had definite signs of bronchopneumonia. The laboratory data were significant because of the presence of severe anemia, thrombocytopenia, and leucopenia with marked left shift in all patients, although three patients had leucocytosis when first seen. No other significant symptoms or signs were noted in these patients.

## DISCUSSION

It seems that there is gradually accumulating more proof that the generalized form of the infection with *H. capsulatum* is not always fatal. The case

herein reported is the fourth one reported so far. Recovery may occur even when the disease is quite severe, as this infant had all the characteristics we have seen in the fatal form, and yet she recovered under nonspecific supportive measures. There is no known therapeutic agent which is effective against this organism. Many have been tried without results.

Fig. 13.

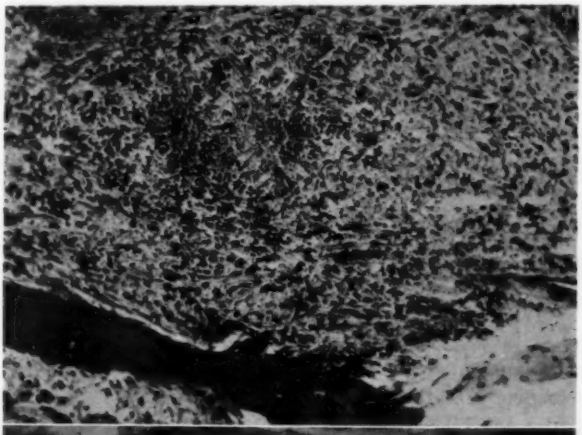

Fig. 14.

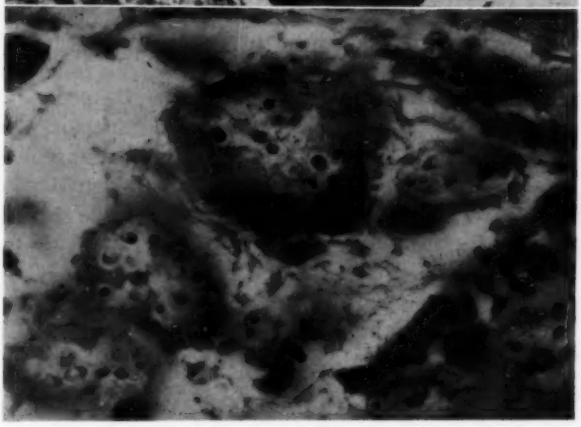

Fig. 13.—Bone marrow (J. A. M.) showing marrow hypoplasia of hemopoietic elements and granulomatous change in case of histoplasmosis. (Low power.)

Fig. 14.—Bone marrow (J. A. M.) showing large macrophages containing the typical organisms *Histoplasma capsulatum*. (Oil immersion.)

This patient also demonstrated the development of a positive skin test after subsidence of her acute illness, and negative skin tests to other fungus antigens. This would further substantiate the heretofore circumstantial evidence that a positive skin test was indicative of disease caused by the *H. capsulatum* organ-

ism. An analogy to tuberculosis seems warranted: that it takes several weeks to months after an initial infection before sufficient antibodies are produced to give a positive skin reaction, and that the positive skin reaction then means that the disease is either active or has been present previously and is quiescent. A negative skin test has been universal in fatal cases as in these presented here and this probably means that either the infection is so overwhelming that no antibodies are produced (similar to the state of energy in miliary tuberculosis) or that the patient dies before sufficient time elapses for the production of antibodies. Cross reactions to other fungus antigens were not found. This would add to the evidence that there is less tendency to cross reactions in human histoplasmosis than there is in experimentally infected animals as reported by Emmons and associates.[14]

The signs and symptoms manifested by the nine patients who died were the same as have been described by all who have written about the disease. The lesions found at autopsy were generalized, but one is struck by the accumulation of lesions in the gastrointestinal tract and the mesenteric lymph nodes and in the lungs and hilar lymph nodes. While the actual mode of infection and portal of entry are unknown, the pathologic lesions would implicate both the gastrointestinal and respiratory tracts. The widespread lesions and the demonstration of intravascular mononuclear cells containing the organisms, plus the ability to culture the organism from the blood, are proof that the disease is spread throughout the body by the blood stream. Wherever reticulo-endothelial cells are to be found, the organisms are found contained in these cells. This disease has rightly been called a reticulo-endothelial cytomycosis.

The use of cultures of bone marrow on Sabouraud's media as a diagnostic agent deserves emphasis. The technique is simple and the results positive fairly quickly. Bone marrow is obtained in the usual way from either the tibia, femur, or iliac crest and may be heparinized or citrated to prevent clotting. Then 0.1 c.c. of the liquid material is made to flow over a Sabouraud slant or blood agar and allowed to stand at room temperature. Since 1947 we have used this technique and have been able to diagnose all cases prior to autopsy. In all, except the growth obtained from the patient who has recovered, the growth of the fungus occurred in from 7 to 10 days so that the typical organism could be recognized in its tuberculate chlamydospore form when examined under a microscope in a saline mixture. Blood cultures may be cultured in the same way, as may material obtained by biopsy of lymph nodes, liver, and spleen.

Two of the patients reported herein had twin siblings die of a disease similar in symptomatology to that of histoplasmosis. The familial occurrence of histoplasmosis has been reported before.[15] We have yet to determine where this organism occurs in nature, whether it can be found in a carrier state, and what the mode of infection of human beings is before true strides can be made in the control of the disease. As stated before, there are no known agents which are therapeutically fungicidal but nontoxic for treatment of the disease in its disseminated form.

SUMMARY

A case of severe generalized histoplasmosis proved by culture of the organism and which has recovered and has been clinically well for eight months is reported. The significance of this in relation to the development of positive skin tests to histoplasmin is discussed.

The manifestations of histoplasmosis in nine other fatal cases are reviewed with special emphasis on the typical signs and symptoms of a respiratory-type disease with hepatosplenomegaly, anemia, leucopenia, left shift, with or without thrombocytopenia.

The advantages of bone marrow culture for early and easy diagnosis are discussed. Megaloblastic anemia, reversible by folic acid, was found in one of the fatal cases.

Subsequent to the writing of this article, a 6-month-old infant was admitted to St. Louis Children's Hospital and died eighteen days later. The history, physical findings, and laboratory data including blood culture and bone marrow culture, were typical for histoplasmosis. An extremely interesting post-mortem finding was noted: On cutting the lung, a typical "primary complex" type of lesion was found with regional lymph node enlargement and caseation. Microscopic section showed it to be a granulomatous lesion containing *Histoplasma capsulatum* organisms. This finding serves to further emphasize the previously drawn analogy of this disease to tuberculosis. As in tuberculosis, histoplasmosis tends to be disseminated in the young infant as if there were no immunity or resistance to the spread of the infection, while in the older child or adult, the disease tends to be localized in the lung and to become calcified in small tubercles. These findings are to be reported more completely at a later date.

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# CARROT SOUP IN THE TREATMENT OF INFANTILE DIARRHEA

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IN the JOURNAL OF PEDIATRICS (**35**: 422, 1949), Smith and Fischer introduced into American pediatrics carob flour in the treatment of severe diarrhea in infants and children. In my paper I wish to draw attention to another antidiarrheic substance of similar effect. This substance seems to be only slightly known and has evidently not been treated in the American pediatric literature

Moro[1] found, in 1907, that carrots had a clear antidyspeptic effect in animal experiments. He obtained extremely good results with children suffering from grave diarrhea by feeding them with soup made from carrots and bouillon. Moro's well-documented investigations attracted some notice,[2] but carrots were soon replaced by apples. After a long time, carrots were rehabilitated, first in Germany.[3-5] Since then results which, on the whole, were extraordinarily good, have also been reported from Sweden,[6] France,[7-9] and Belgium.[10] In spite of this experience carrot soup does not seem to be so widely employed as its superior antidiarrheic qualities merit.

The carrot soup which I have found to be most suitable is prepared in the following manner: 500 Gm. preferably fresh carrots are washed and well scraped. They are finely chopped, and cooked with 150 Gm. water in a pressure cooker for fifteen minutes. The entire pulp is then passed through a fine strainer and diluted with hot water up to one liter, and 3 Gm. common salt are added. Fresh soup is made every day.

Immediately after hospitalization children suffering from diarrhea receive this soup in as large amounts as possible. After twenty-four hours milk can be given. The youngest children receive skim breast milk and the others skim citric-acid milk corresponding to approximately one-fifth of the caloric requirement. The amount of milk is increased daily and the carrot soup is gradually reduced. The children receive carrot soup for from seven to ten days. No fasting is necessary.

On account of the consistency of the soup it must be administered by spoon. For bottle- or tube-feeding the soup must be diluted with about one-third fluid (tea or Ringer's solution). I have used this soup in treating children who weighed as little as 1,200 grams. The soup can also be employed to great advantage in cases of acute enteritis, both in older children and adults. As a rule, children eat it readily. It affords an evident feeling of satiation. Parenteral administration of fluid is seldom necessary.

After about only twelve hours' treatment there is a marked change in the condition of the children. In infants with toxicosis the improvement is often dramatic. Vomiting if any, ceases at once, the acidosis and symptoms of dehydration disappear; the appetite returns and the usual milk mixtures are

From the Children's Department, Kristianstad and the Flensburg Children's Hospital, Malmö.

well tolerated. A marked increase in weight is generally seen in cases of dehydration. The feces change promptly: after from twelve to twenty-four hours carrots appear, at first combined with a fair amount of mucus. About twenty-four hours later they consist of dry, yellowish-red, voluminous masses of carrot.

The antidiarrheic effect of carrots is probably due largely to their pectin content as is the case with apples, bananas, and tomatoes, which are used in a similar way. In all these diets there is also probably a mechanical removal of the infected intestinal contents, and bacteria are prevented from migrating up to the duodenum and the stomach as occurs in severe dyspeptic conditions, Furthermore, carrots are rich in minerals,[11] which are of utmost importance in cases of dehydration and acidosis due to diarrhea.[12, 13] The potassium and phosphorus content of carrots is 2.5 times as high as that in apples. The corresponding figure for calcium is 14, for sodium is 40, for magnesium is 3, and for chlorine is 45; plus the sodium chloride that is added in the preparation of the soup.

There are hardly any side-effects to report from the use of carrot soup. In children weighing less than 1,500 grams ileus-conditions may develop from profuse administration of the soup. Edema is seen now and then during the first few days but disappears rapidly.

Since 1944 I have used carrot soup in about 450 cases of diarrhea, particularly in infants. The mortality rate is approximately 2 per cent. If the four children who died within five hours after entering the hospital are excluded, the mortality is less than one per cent. For the correct evaluation of this figure, which is very low when compared to, for example, figures from Central Europe, one should bear in mind the good nutritional condition of Swedish children during these years, the absence of epidemic diarrhea of the newborn infants, as well as the almost entire lack of Salmonella and dysentery infections.

The last twenty-four infants with toxicosis treated with carrot soup are tabulated in Table I, arranged according to weight. In most of these patients dehydration was so severe that parenteral administration of fluid was considered necessary. Table I indicates the low mortality rate, the tolerance of the soup by even young infants, the prompt recovery, and the frequently marked increase in weight.

## CONCLUSION

Carrot soup is an extremely reliable, easily obtainable, and simple, nourishing substance which acts promptly in the treatment of acute diarrheal disturbances in infants. In my own experience, I have found carrot soup to be far superior to all substances hitherto employed. It can be given even to premature babies. In the last twenty-four cases of toxicosis treated there was only one fatality.

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TABLE I.

| WEIGHT ON DAY OF ADMINISTRATION OF CARROT SOUP (GM.) | AGE | NO. OF DAYS OF ILLNESS BEFORE ADMINISTRATION OF CARROT SOUP | NO. OF DAYS OF TREATMENT BEFORE FORMED STOOLS APPEARED | GAIN OR LOSS IN WEIGHT DURING FIRST SEVEN DAYS (GM.) | FLUID REPLACEMENT THERAPY (ML.)* | OTHER THERAPY | OUTCOME |
|---|---|---|---|---|---|---|---|
| 1,430 | 13 days | 2 | 2 | + 250 | Ringer 220, blood 34 | Sulfa | Cured |
| 1,530 | 19 days | 2 | 5 | + 30 | Ringer 550, blood 40 | Penicillin | Cured |
| 1,880 | 9 days | 1 | 2 | 0 | Ringer and Dextrose 405, blood 20 | Penicillin | Cured |
| 2,160 | 1 month | 2 | 2 | + 400 | Ringer 140, blood 65 | Sulfa | Cured |
| 2,460 | 1 month | 1 | 2 | − 120 | Ringer 105, blood 35 | Penicillin | Cured |
| 2,520 | 2 months | 3 | 2 | + 620 | Ringer 50 | | Cured |
| 3,020 | 1 month | 1 | 2 | + 680 | Ringer 100 | Penicillin | Cured |
| 3,110 | 3 weeks | 1 | 1 | + 410 | Ringer 40 | Penicillin, sulfa | Cured |
| 3,140 | 1 month | 1 | 1 | + 460 | Ringer 165, blood 110 | Sulfa | Cured |
| 3,300 | 6 weeks | 5 | 2 | + 680 | Ringer 110 | Penicillin | Cured |
| 3,320 | 7 weeks | 1 | 2 | + 480 | Ringer 80 | Sulfa | Cured |
| 3,530 | 7 weeks | 2 | 1 | + 10 | Ringer 290, blood 80 | Penicillin | Cured |
| 3,630 | 6 weeks | 3 | 1 | + 360 | Ringer 195, blood 60 | Penicillin, sulfa | Cured |
| 3,740 | 1 month | 1 | 2 | + 460 | Ringer 80 | Sulfa | Cured |
| 4,750 | 7 weeks | 1 | 2 | + 550 | Ringer 95, blood 40 | Penicillin, sulfa | Cured |
| 5,200 | 3 months | 4 | 2 | + 340 | Ringer 180 | Sulfa | Cured |
| 5,280 | 2 months | 5 | 2 | + 420 in 6 days | Ringer 70 | Penicillin | Fatal with fever and convulsions on sixth day |
| 5,450 | 4½ months | 4 | 3 | + 850 | Ringer 160, blood 200 | Sulfa | Cured |
| 6,220 | 6 months | 1 | 1 | − 20 | | Sulfa | Cured |
| 6,400 | 4½ months | 1 | 2 | + 380 | Ringer 60 | | Cured |
| 6,640 | 6 months | 7 | 3 | + 360 | | Sulfa | Cured |
| 7,100 | 7 months | 1 | 2 | + 50 | Ringer 55 | Penicillin | Cured |
| 8,500 | 10 months | 1 | 1 | + 680 | Ringer 150, blood 100 | Penicillin, sulfa | Cured |
| 8,140 | 9 months | 1 | 1 | + 560 | | Penicillin | Cured |

*Ringer=Ringer's solution.

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# CONGENITAL ANORECTAL STRICTURE

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THE subject of congenital anorectal stricture or stenosis seemed important enough to warrant further study. We have examined 100 consecutive infants brought to the well-baby clinic for routine care. They were all newborn infants attending the clinic for the first time at 3 or 4 weeks of age.

A digital rectal examination was done on each infant. If an anorectal stricture was found, the mother was asked to bring the child to the clinic at monthly intervals for at least six months. Our aim was to gather accurate statistics regarding the incidence of anorectal constriction, the frequency and the character of symptoms caused by it, and the fate of the lesion itself when left untreated.

At each subsequent visit the rectal examination was repeated and the mother was questioned again about the child's appetite, the incidence of vomiting, the kind of stools passed, and the occurrence of crying or straining when passing a stool or at any other time.

The purpose of this paper is first to report the results of this investigation and second to discuss the entire subject of anorectal stricture, a condition which we have encountered frequently in private practice.

Thirty-nine (39 per cent) of the infants in the clinic were found to have positive evidence of anorectal stricture on digital examination. In only nine of these (23 per cent), was there a history of excessive straining and crying when having a bowel movement. The stools were described as hard in one infant. The crying was excessive in three and in each of these anal fissures were present. Seven of the nine infants having difficulty passing stools were also restless during the greater part of the day. Bleeding with a bowel movement was present in one of the babies. There was no vomiting or loss of appetite in any of the patients. Eleven of the infants bled when examined even though every effort was made not to force the examining finger into the rectum beyond the point where the first sign of stricture became apparent. Although it was not our intention to treat any of these children, one had to be treated because of the severity of the symptoms.

Monthly follow-up studies showed that the stricture in all except one (the one treated) dilated spontaneously sometime between 3 and 6 months of age. The symptoms persisted as long as there was any constriction present, but became less severe as the stricture dilated.

It is apparent from this study that anorectal stricture occurs rather frequently in newborn infants. Fortunately, however, the condition gave rise to symptoms in only about one in four afflicted with it. It moreover proves

From the Pediatrics Service of Dr. Benjamin Kramer, The Jewish Hospital of Brooklyn.

TABLE I. RELATIVE NUMBER OF STRICTURES FOUND IN WHITE AND NEGRO INFANTS

| INFANTS | NO. OF CASES | NO. OF CASES WITH STRICTURE | PER CENT |
|---|---|---|---|
| White | 19 | 9 | 47.3 |
| Negro | 81 | 30 | 37.0 |

TABLE II. RELATIVE NUMBER OF STRICTURES FOUND IN MALE AND FEMALE INFANTS

| INFANTS | NO. OF CASES | NO. OF CASES WITH STRICTURE | PER CENT |
|---|---|---|---|
| Males | 51 | 21 | 41.1 |
| Females | 49 | 18 | 36.7 |

without doubt that the stricture tends to correct itself. Similarly, the symptoms associated with this lesion disappear but are a source of discomfort to the infant while they persist.

## DISCUSSION

Congenital anorectal stricture is one of the most common abnormalities found in infants. This fact is not generally recognized because the condition is relegated to a minor role in the literature and textbooks dealing with the general subject of congenital malformations of the rectum and anus. Its importance becomes apparent, however, when one realizes the frequency with which it causes restlessness, crying, abdominal distention, and difficulty with bowel movements in the early weeks of the child's life.

Webb found a ringlike constriction just above the internal sphincter in 19 instances (12.6 per cent), in a consecutive series of 150 infants delivered in the Shreveport Charity Hospital. Zahorsky examined 60 young infants and found a palpable anorectal ring in 15 cases (25 per cent). Of 61 cases of anorectal conditions in infants and young children seen by Liburt, he found 22 had congenital anal stricture. In our own series of 100 infants, the constriction was found 39 times (39 per cent). In only 9, however, were there symptoms associated with the stricture.

Anorectal stricture is due to an incomplete absorption of the membrane formed by the fusion of the hind gut and proctoderm between the eighth and ninth week of fetal life. The persistence of some or most of this embryonic membrane gives rise to a constriction of the lumen of the bowel, varying in size and shape according to the amount that fails to be absorbed. The membrane is composed principally of mucosa and submucosa and is usually found 2 to 3 cm. (¾ to 1⅛ inches) from the anus.

Apparently not all strictures are tight enough to give rise to symptoms, for only 9 of our 39 infants with demonstrable constriction suffered because of this abnormality. Some difficulty in expelling the stool is present in every case of stricture causing symptoms. At the time of defecation, the child strains excessively; turning red or blue in the face and usually crying. The mother is surprised to see her child work so hard to pass a soft or even loose stool. Such a history is very significant and in most instances is pathognomonic of anorectal stricture. One can almost always predict the presence of

this abnormality when such a history is obtained from the mother. The stools passed are sometimes pencil- or ribbon-shaped. As they become firmer and more difficult to pass, constipation increases, resulting in abdominal distention due to retained feces and gas and causing great discomfort to the infant. Most of these infants keep bearing down even when the rectum is empty, probably because the persistent membrane gives the child the feeling that something foreign is present which requires repeated efforts to remove it.

The diagnosis of anorectal stricture is easily made by inserting a finger into the rectum. This should be done in every infant when the mother reports that the child is having difficulty in passing his stool. There will be some degree of resistance to passage of the finger in these infants, where as normally the finger passes into the rectum with ease even in very small infants. Infants with stricture cry when being examined and usually strain in the same manner as when passing a stool. With the withdrawal of the examining finger, there is usually the passage of a normal-looking stool frequently covered with various amounts of blood, due, of course, to unavoidable trauma accompanying the examination. It is wise to warn the mother about the probability of such bleeding. This will allay her fears and avoid embarrassment to the examiner if such bleeding does take place. One can frequently avoid such bleeding if the finger is introduced no further than the point at which resistance to its advance is met. The finding of such resistance with a suggestive history is all that is required for the diagnosis of the condition.

Very often the mother will not volunteer information about her child's difficulty in passing stools. It is important, therefore, to question her about this in every case where there is a history of excessive crying (colic), constipation, or abdominal distention.

The stricture tends to correct itself after three to six months in most instances. This was shown in our series where in all but one it dilated spontaneously and the symptoms disappeared somewhere between 3 and 6 months of age. During this time, however, these infants were uncomfortable. Treatment of these infants as soon as the condition was found would have given certain relief to the difficulty in passing the stool and probable relief to any associated colic.

The use of laxatives, enemas, and suppositories by mothers to obtain relief will often establish the habit of constipation in their children, which may continue to all ages of adult life.

Some of these strictures are tight enough to give rise to symptoms of acute or subacute intestinal obstruction. Brennemann reported six cases in young infants with a picture of abdominal distention, constipation, and great distress; all were promptly relieved by dilatation of an anorectal stricture.

Sincock and Wells presented a case of a 7-month-old infant with a large palpable mass in the right side of the abdomen, diagnosed by nine pediatricians as a neoplastic process. Autopsy, however, showed the cause of death to be intestinal obstruction resulting from congenital anal stenosis and a complicating fecal impaction.

Occasionally anorectal constrictions are found in older children and in adults. David reported the condition in patients 16 months, 4 years, and 7 years

of age, respectively. Reclus, in 1913, reported six cases in adults from 32 to 52 years of age, all with a diaphragmatic constriction about 3 cm. above the anal orifice.

Only strictures giving rise to associated symptoms in infants should be treated. Most authors agree that the stricture can be cured by simple dilatation with a well-lubricated finger at intervals of one day to a week over a period of weeks or months. The treatment is continued until the index finger may be inserted freely. In patients resisting this form of treatment, it is suggested that multiple incisions of the membrane be made.

Our experience, however, has taught us that digital dilatation of anorectal stricture is a very crude method, giving rise to much pain and bleeding in most cases, even though every effort is made to be gentle and careful. This form of treatment is a frightening experience for the mothers and few bring the infants back for subsequent dilatation. We have, therefore, abandoned this form of therapy.

For nearly two years we have been using a set of flexible rubber dilators* graduated in three sizes for the treatment of anorectal stricture in infants. In most cases the membrane can be stretched at one visit by inserting the three dilators, starting with the smallest and stepping up to the largest size. Each dilator is well lubricated before use with a specially processed oil base (Fig. 1) combined with benzocaine 4.5 per cent, carbolic acid 1.75 per cent, menthol 0.5 per cent, ephedrine 0.125 per cent.† This combination affords immediate symptomatic relief, thereby reducing the discomfort to the infant during and immediately following the dilatation. Mothers are also asked to insert this anesthetic oil once or twice at home if the infants are disturbed too much by the office procedure.

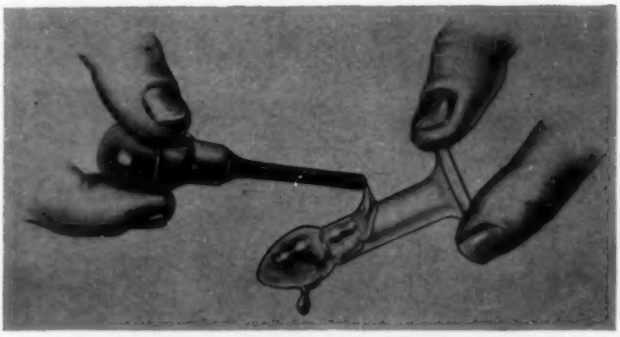

Fig. 1.—Liquid topical analgesic being applied to flexible rubber dilator.

For treatment with the dilators, the child is placed on his back with knees flexed and somewhat drawn up. The smallest dilator is then gently inserted as far as its base (Fig. 2), holding the dilator in place for several minutes by

*Flexible rubber dilators, supplied through courtesy of F. E. Young and Company, Chicago.

†Rectalgan, supplied through courtesy of Mallon Division of Doho Chemical Corporation.

pressing the buttocks against it with the fingers of one hand (Fig. 3). When this is accomplished, the next size is similarly employed and held in place for a few minutes. This middle-sized dilator is inserted and withdrawn several times before the largest dilator is used.

Fig. 2.—Flexible rubber dilator being inserted into infant's rectum.

Fig. 3.—Dilator being held in place by pressing the buttocks against it with the fingers of one hand.

The entire procedure is accomplished with very little, if any, bleeding and the minimum of discomfort to the infant. Frequently there is no bleeding at

all. The rare case of excessive bleeding can be controlled by local pressure with gauze. Occasionally a small rectal prolapse will follow the withdrawal of the dilators. This can be avoided by continuing to hold the buttocks tightly, as described above, for a short time after each dilator is removed.

Most of the infants are completely relieved by this single-stage treatment. Once in a while there will be only partial relief and it may be necessary to repeat the dilatation with the largest dilator at a subsequent visit. Not once in our experience was it found necessary to resort to surgery to accomplish a cure.

## SUMMARY

1. Congenital anorectal stricture was found in 39 of 100 consecutive infants brought for routine care to the well-baby clinic.

2. Only 9 of the 39 strictures gave rise to associated symptoms.

3. All the strictures dilated spontaneously if left untreated when the infants reached the age somewhere between 3 and 6 months.

4. Strictures giving rise to associated symptoms should be treated to give the infants relief.

5. Treatment is best accomplished by single-stage dilatation with flexible rubber dilators* lubricated with a liquid, topical analgesic.†

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*Flexible rubber dilators supplied through courtesy of F. E. Young and Company.
†Rectalgan, supplied through courtesy of Mallon Division of Doho Chemical Corporation.

# ANTIBIOTIC SPECTRUM OF HEMOPHILUS PERTUSSIS

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THE data that are reported in this paper were obtained as part of a series of investigations into what might be called the antibiotic spectra of a variety of species of human pathogenic bacteria that are concerned in some of the common infectious diseases. This report deals with the results of in vitro tests for sensitivities that were carried out on recently isolated strains of *Hemophilus pertussis* with nine antibiotics, namely, penicillin, streptomycin, bacitracin, polymyxin, aerosporin, aureomycin, Chloromycetin, neomycin, and terramycin. These tests were done in conjunction with therapeutic trials of new antibiotics in cases of pertussis. A preliminary report of the effects of aureomycin on the course of this disease is reported separately.[1]

## MATERIALS AND METHODS

The strains of *H. pertussis* used in this study were obtained from nasopharyngeal swab cultures of active cases of whooping cough before any antibiotic therapy was given. Bordet-Gengou medium containing 20 per cent fresh, defibrinated sheep's blood was used throughout. Characteristic colonies were picked and pure cultures from single colonies were isolated and then maintained by repeated subculture until the tests were done. The organisms were identified by their colonial and morphologic characteristics and by slide agglutinations in specific antiserum.

For the sensitivity tests each strain was heavily seeded on a plate and after seventy-two hours' incubation at 37° C., the surface growth was harvested with a 5 mm. loop into 1 ml. of either physiologic salt solution or broth. Plates containing the same media but incorporating serial twofold dilutions of each antibiotic were then prepared.

Each plate was divided into from six to ten segments and the individual culture suspensions were streaked on these segments with a 2 mm. loop. Each loopful contained roughly between $10^8$ and $10^9$ organisms as estimated from surface pour plates. With the exception of Chloromycetin, all of the dilutions of antibiotics were freshly prepared from the dry preparations prior to each test; a standard solution of Chloromycetin was kept in the frozen state at −25° C. and used for all of the tests. Because of the tendency of aureomycin to deteriorate rapidly in neutral or alkaline solutions, special care was taken to make the dilutions of this antibiotic immediately before the plates were poured and the plates were streaked quite promptly after they solidified. This method which is similar to that used by Bradford and Day[2] was essentially the same as the plate-dilution method used in this laboratory for other organisms[3] and was modified only by the use of media and length of incubation suitable for *H. pertussis*. The plates were incubated for seventy-two hours and the growth recorded after close inspection in suitable light and with the aid of an engraver's glass (3×). Standard strains were included in each test as a control on the activity of the antibiotic and the validity of the tests.

The sensitivity of each organism was defined as the minimum concentration of antibiotic on which there was complete inhibition of growth, that is, no growth whatever was

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discernible at seventy-two hours. The value for partial inhibition was considered to be the minimum concentration of antibiotic on which marked but incomplete inhibition of growth occurred as evidenced by the growth of only a few individual colonies or of a moderate or large number of very minute colonies.

The following antibiotic preparations were used:

Crystalline penicillin G (potassium salt) (C.S.C.), 1,595 units per milligram
Streptomycin (calcium chloride complex) (Merck)
Bacitracin, 34 units per milligram*
Polymyxin (Polymyxin D) hydrochloride (Lederle, B 71)†
Aerosporin (Polymyxin B) hydrochloride‡
Crystalline aureomycin hydrochloride†
Crystalline Chloromycetin (chloramphenicol)§
Neomycin sulfate, 173 units per milligram*
Crystalline terramycin hydrochloride‡

Groups of 10 or more organisms were tested simultaneously with from three to seven antibiotics so that the same media, culture suspensions, and antibiotic dilutions were employed in each test.

## RESULTS

The values for the sensitivity of each of 31 strains of *H. pertussis* tested with the seven antibiotics which had been used in similar studies with other organisms[3] are listed in Table I. Neomycin and terramycin became available after the tests with these 31 strains were completed. Additional strains were then collected and tested with these new antibiotics. Since some of the results listed in Table I, particularly those obtained with streptomycin and aureomycin, did not correspond very closely with those reported by others,[2] these two antibiotics as well as penicillin and Chloromycetin were also included at the time when the tests with the new agents were carried out. The results are listed in Table II.

The concentrations of any one of the antibiotics which were required to inhibit completely all of the strains, fell largely within a rather narrow range except in the case of streptomycin and bacitracin. This is shown more clearly in Fig. 1 in which these data are summarized graphically by representing the cumulative distribution of the sensitivities of all of the strains tested with each antibiotic in a curve. This figure may be considered as a sort of "antibiotic spectrum" of *H. pertussis*, each antibiotic being represented by a band or curve in this spectrum. From this figure one can compare the in vitro sensitivity of these organisms to the various antibiotics, or to put it another way, the relative in vitro activity of the different antibiotics against these strains. On a weight basis the order of their effectiveness, according to these data is: 1) polymyxin, 2) aerosporin, 3-5) Chloromycetin, aureomycin, and terramycin, which have very similar activity against the great majority of the strains, 6) penicillin, 7) streptomycin, 8) neomycin, and 9) bacitracin.

With respect to streptomycin and aureomycin, these results are at variance with those of Bradford and Day[2] who reported higher values for aureomycin and lower ones for streptomycin. The reasons for the discrepancies are not

*Supplied by Dr. Lawrence W. Smith of Commercial Solvents Corp.
†Furnished by Dr. Stanton M. Hardy of Lederle Laboratories.
‡Provided by Dr. Gladys L. Hobby of Chas. Pfizer & Co., Inc.
§Obtained from Dr. E. A. Sharp of Parke, Davis & Co.

TABLE I. SENSITIVITY OF THIRTY-ONE STRAINS OF *Hemophilus pertussis* TO SEVEN ANTIBIOTICS*

| STRAIN | PENICILLIN | STREPTOMYCIN | BACITRACIN | POLYMYXIN | AEROSPORIN | AUREOMYCIN | CHLOROMYCETIN |
|---|---|---|---|---|---|---|---|
| 1 | 1.0 | 2.5 | 60 | 0.16 | 0.16 | 0.31 | 0.63 |
| 2 | 1.0 | 10.0 | 60 | 0.16 | 0.08 | 1.25 | 0.63 |
| 3 | 1.0 | 2.5 | 120 | 0.16 | 0.08 | 0.16 | 0.16 |
| 4 | 1.0 | 10.0 | 120 | 0.16 | 0.31 | 0.63 | 0.63 |
| 5 | 0.5 | 10.0 | 120 | 0.16 | 0.31 | 0.63 | 0.63 |
| 6 | 2.0 | 5.0 | 120 | 0.31 | 0.63 | 0.31 | 0.63 |
| 7 | 1.0 | 2.5 | 120 | 0.16 | 0.16 | 0.31 | 0.63 |
| 8 | 0.5 | 5.0 | 30 | 0.08 | 0.16 | 0.31 | 0.63 |
| 9 | 0.5 | 20.0 | 30 | 0.08 | 0.16 | 1.25 | 0.63 |
| 10 | 1.0 | 10.0 | 60 | 0.16 | 0.16 | 1.25 | 0.63 |
| 11 | 2.0 | 10.0 | 30 | 0.16 | 0.63 | 0.63 | 0.63 |
| 12 | 0.5 | 10.0 | 60 | 0.16 | 0.31 | 0.63 | 0.63 |
| 13 | 1.0 | 40.0 | 30 | 0.16 | 0.31 | 0.63 | 0.63 |
| 14 | 1.0 | 40.0 | 15 | 0.08 | 0.63 | 0.63 | 0.63 |
| 15 | 1.0 | 40.0 | 15 | 0.16 | 0.16 | 1.25 | 0.63 |
| 16 | 2.0 | 40.0 | 30 | 0.16 | 0.16 | 1.25 | 0.63 |
| 17 | 1.0 | 80.0 | 120 | 0.16 | 0.63 | 1.25 | 0.63 |
| 18 | 1.0 | 2.5 | 30 | 0.16 | 0.31 | 2.5 | 0.63 |
| 19 | 1.0 | 10.0 | 200 | 0.5 | 1.0 | 1.0 | 1.25 |
| 20 | 1.0 | 5.0 | 100 | 0.5 | 0.25 | 1.0 | 1.25 |
| 21 | 1.0 | 20.0 | 100 | 0.5 | 0.25 | 1.0 | 1.25 |
| 22 | 2.0 | 20.0 | 200 | 1.0 | 0.25 | 1.0 | 1.25 |
| 23 | 2.0 | 10.0 | 200 | 1.0 | 0.5 | 1.0 | 1.25 |
| 24 | 2.0 | 10.0 | 200 | 0.5 | 1.0 | 2.0 | 2.5 |
| 25 | 1.0 | 20.0 | 200 | 0.5 | 1.0 | 2.0 | 1.25 |
| 26 | 1.0 | 10.0 | 200 | 0.5 | 0.5 | 2.0 | 2.5 |
| 27 | 1.0 | 40.0 | 200 | 0.5 | 1.0 | 1.0 | 1.25 |
| 28 | 1.0 | 20.0 | 200 | 0.5 | 1.0 | 2.0 | 2.5 |
| 29 | 1.0 | 10.0 | 200 | 0.5 | 0.5 | 2.0 | 1.25 |
| 30 | 1.0 | 20.0 | 200 | 0.5 | 0.5 | 1.0 | 1.25 |
| 31 | 1.0 | 20.0 | 200 | 0.5 | 0.5 | 1.0 | 1.25 |

*All sensitivities expressed as minimum concentration in micrograms per milliliter required for complete inhibition of growth in seventy-two hours.

TABLE II. SENSITIVITY OF TWENTY-FOUR ADDITIONAL STRAINS OF *Hemophilus pertussis* TO VARIOUS ANTIBIOTICS*

| STRAIN | PENICILLIN | STREPTOMYCIN | AUREOMYCIN | CHLOROMYCETIN | NEOMYCIN | TERRAMYCIN |
|---|---|---|---|---|---|---|
| 32 | 1.6 | 3.1 | 0.1 | 8.0 | 150. | 6.3 |
| 33 | 1.6 | 25. | 12.5 | 8.0 | 9. | 12.5 |
| 34 | 1.6 | 3.1 | 1.6 | 1.0 | 9. | 6.3 |
| 35 | 1.6 | 1.6 | 0.1 | 0.3 | 9. | — |
| 36 | 1.6 | 25. | 0.1 | 0.3 | 9. | 0.8 |
| 37 | 1.6 | 25. | 0.8 | 2.0 | 5. | 0.8 |
| 38 | 1.6 | 12.5 | 0.1 | 0.3 | 9. | — |
| 39 | 1.6 | 12.5 | 1.6 | 0.3 | 9. | 12.5 |
| 40 | — | — | — | — | 5. | — |
| 41 | 1.6 | 3.1 | 0.1 | 0.3 | 9. | 6.3 |
| 42 | 1.6 | 1.6 | 0.1 | 0.3 | 9. | 0.4 |
| 43 | 1.6 | 1.6 | 0.1 | 1.0 | — | — |
| 44 | 0.8 | 3.1 | 0.8 | 0.8 | 12.5 | 0.4 |
| 45 | 0.8 | 1.6 | 0.8 | 0.8 | 12.5 | 0.2 |
| 46 | 0.8 | 3.1 | 0.8 | 0.8 | 12.5 | 0.4 |
| 47 | 0.4 | 0.8 | 0.8 | 0.8 | 12.5 | 0.4 |
| 48 | 0.4 | 3.1 | 0.4 | 0.8 | 25. | 0.4 |
| 49 | 0.4 | 3.1 | 0.4 | 0.4 | 25. | 0.4 |
| 50 | 0.4 | 3.1 | 3.1 | 0.8 | 25. | 0.8 |
| 51 | 1.6 | 3.1 | 1.6 | 0.4 | 25. | 0.4 |
| 52 | 0.8 | 3.1 | — | — | 100. | — |
| 53 | 0.8 | 3.1 | 1.6 | 0.4 | 100. | 0.4 |
| 54 | 0.8 | 3.1 | 0.4 | 0.4 | 12.5 | 0.4 |
| 55 | 0.8 | 3.1 | — | — | — | — |

*Sensitivities expressed in micrograms per milliliter required for complete inhibition of growth in seventy-two hours; — = not done.

readily apparent since essentially the same methods were used. In the present study, similar results were obtained in tests carried out at different times. Furthermore, the results obtained on the same plates with a standard laboratory strain of *Klebsiella pneumoniae* that was included with each test were fairly uniform within the limits of this method and were similar to those regularly observed with this strain in other tests with both streptomycin and aureomycin.

In the case of the streptomycin sensitivities of the pertussis strains, several of the high values may be the result of emergence of resistant variants which appeared in some of the higher concentrations. With this antibiotic also, the range of "partial inhibition" was wider than was the case with any of the other antibiotics. Furthermore, only with this agent were "skips" observed in the range of partial inhibition; that is, there was no growth discernible on plates containing some of the dilutions of streptomycin that were intermediate between the minimum complete inhibiting concentration and the concentrations showing full growth or nearly full growth. This may be related to the relatively large number of organisms used for the inoculum in these tests.[4]

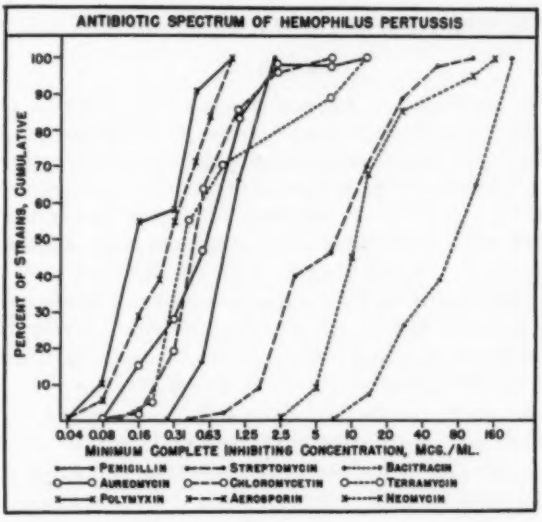


Fig. 1.

In order to indicate the differences in the sharpness of the end points of inhibition obtained with the different antibiotics, the ranges of partial inhibiting concentrations have been summarized in Table III. It is seen that with most of the antibiotics and for most of the strains, the ratio of the complete to the partial inhibiting concentrations was either 1 or 2, that is, there was either a sharp end point or at most only a single dilution showing partial inhibiton. In the case of bacitracin, however, 10 of the 31 strains showed a wider range of partial inhibiting concentration, while with streptomycin, only a few strains

TABLE III. SUMMARY OF RESULTS OF SENSITIVITY TESTS ON STRAINS OF *Hemophilus pertussis* WITH NINE ANTIBIOTICS

| ANTIBIOTIC | NUMBER OF STRAINS TESTED | RANGE OF MINIMUM COMPLETE INHIBITING CONCENTRATIONS (μG/ML.) | NUMBER OF STRAINS FOR WHICH THE RATIO OF COMPLETE TO PARTIAL INHIBITING CONCENTRATIONS WAS: | | | | |
|---|---|---|---|---|---|---|---|
| | | | 1 | 2 | 4 | 8 | 16 |
| Penicillin | 54 | 0.4-2.0 | 20 | 29 | 4 | 1 | — |
| Streptomycin | 54 | 0.8-80. | 7 | 16 | 10 | 12 | 9 |
| Bacitracin | 31 | 16.-200. | 5 | 16 | 9 | 1 | — |
| Polymyxin | 31 | 0.08-1.0 | 10 | 18 | 3 | — | — |
| Aerosporin | 31 | 0.08-1.0 | 10 | 16 | 5 | — | — |
| Aureomycin | 52 | 0.16-12.5 | 9 | 29 | 10 | 4 | — |
| Chloromycetin | 52 | 0.16-8.0 | 15 | 32 | 4 | 1 | — |
| Neomycin | 22 | 5-150 | 10 | 9 | 2 | 1 | — |
| Terramycin | 18 | 0.2-12.5 | 3 | 3 | 3 | 7 | 2 |

showed sharp end points whereas 31 of the 54 strains tested showed partial inhibition over a 4- to 16-fold range of concentrations. Those with the wider ranges of partial inhibition include the strains with which the "skips" were observed. A similar situation obtains with regard to the new antibiotic terramycin; two-thirds of the strains showed incomplete inhibition over a 4- to 16-fold range and skips were observed in some of the tests with this agent.

## DISCUSSION

The in vitro sensitivity of bacteria to any given antibiotic is only a single index of its possible usefulness in the treatment of infections due to those organisms. The findings presented here are intended to compare, insofar as that is possible by in vitro tests, the activity of a group of antibiotics against a number of recently isolated strains of *H. pertussis*. It is well known that many of the conditions under which such tests are carried out may influence the results, and these conditions vary considerably with the different antibiotics. In the present tests, the choice of media and the conditions of incubation were limited by the growth characteristic of the organism in vitro. While these conditions may influence the activity of each of the antibiotic agents in different ways, the same conditions do not necessarily prevail in the infected host.

Furthermore, many factors in the host such as absorption, diffusion, plasma binding, excretion, and inactivation of the antibiotic may influence the effective concentrations attainable at the site of the infection, and hence the therapeutic efficacy of the agent against the infection. These host factors also vary markedly for the different antibiotics, as does also the toxicity of the agents. The latter alone may indeed be the determining factor in the practical usefulness of an agent for therapeutic purposes. This is well exemplified in polymyxin and aerosporin which, although they are the most effective agents in vitro against almost all of the pathogenic gram-negative bacilli, are nevertheless of only very limited therapeutic value because of their marked toxicity in the effective dose range.

The results of these tests can, therefore, serve only as a first approximation of the efficacy of the different antibiotics and as a preliminary means of comparing their possible usefulness for therapeutic purposes. Only direct clinical trials under controlled conditions can determine their absolute and relative values.

In interpreting the relative position of neomycin and streptomycin in the spectrum, allowance must be made for the fact that the former was not a pure crystalline product. On the basis of the arbitrary dilution units that have been used in standardizing the neomycin, it would appear to be slightly more active than streptomycin. The bacitracin unit, likewise, is an arbitrary one, and the exact position of the curve representing that antibiotic in this spectrum depends on the proporton of active material present in the particular lot used in these tests.

Furthermore, any quantitative comparisons of the values presented in this study with those obtained by others in similar studies will be influenced by the details of the methods used. Wide variations may result from seemingly minor differences in the technique of carrying out the tests or of reading the results. These variations are wider with some antibiotics than with others.

## SUMMARY

The results of in vitro tests for sensitivity of recently isolated strains of *Hemophilus pertussis* to nine antibiotics were presented. The most active of these, on a weight basis and under the conditions of these tests, were polymyxin (Polymyxin D) and aerosporin (Polymyxin B), and both of these agents were about equally active. Chloromycetin, aureomycin, and terramycin ranked next in effectiveness and these three agents also had essentially equal activity. Penicillin was about as active as the three latter agents, but streptomycin and neomycin were appreciably less active. Bacitracin was the least effective in these tests. Some of the difficulties of interpreting these in vitro findings were discussed, particularly with respect to their therapeutic implications.

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# OBSERVATIONS ON A SMALL OUTBREAK OF INFANTILE DIARRHEA ASSOCIATED WITH PSEUDOMONAS AERUGINOSA

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IN 1882 *Pseudomonas aeruginosa* was first described by Gessard.[1] Since then there have been numerous reports of gastroenteritis in young infants due to this bacterium. Recently its importance as a pathogen has been emphasized. In 1947, Hunter and Ensign[2] described an epidemic of twenty-four cases in a nursery for newborn infants which resulted in nine deaths. In 1948, Schaffer and Oppenheimer[3] reported eight cases, five of which were seen between 1945 and 1947, with seven deaths.

It is the purpose of the present communication to report a small outbreak of relatively mild diarrhea with special reference to the results of certain serologic studies. Incidently our efforts at therapy with sulfadiazine, streptomycin, and Polymyxin B will be described, as well as an experiment to determine an effective method of preventing the transmission of *Ps. aeruginosa* by contact.

## EPIDEMIOLOGY

On April 30, 1948, Patient I, who had been admitted five weeks before because of an upper-respiratory infection and aphthous stomatitis, began to have diarrhea. On May 5, the first positive culture for *Ps. aeruginosa* was obtained from his stool. The following day the stools of Patient II who had had recurrent diarrhea since birth, but who had also been in the hospital for five weeks, were reported to contain *Ps. aeruginosa* for the first time. This child was in a cubicle directly across the ward from the first patient. Despite special precautions to avoid further contamination, during the succeeding three weeks, at least four more patients developed diarrhea associated with this organism. In Fig. 1 the dates of first appearance of symptoms and positive cultures for five of the patients are presented graphically. It is noteworthy that two of the later patients (IV and V), who developed their diarrhea at home, had been on the ward because of pulmonary infections during the period when there were at least two patients with active diarrhea associated with *Ps. aeruginosa*. We do not know how many of the other children who had been on the ward at the same time also developed diarrhea at home. On May 20, rectal swab cultures were made on all the other patients then on the ward without detecting any carriers. At the same time the hands of all of the house staff and nurses working with the children were cultured. Positive cultures were obtained from the hands of two of the nurses, Miss T. and Miss D., both of whom had shortly before handled children who had positive stool cultures for *Ps. aeruginosa*. The formulas, bottles, nipples, and forceps for the nipples were also cultured. A positive culture was obtained from a nipple forceps which had presumably been kept in 70 per cent alcohol. (None of this solution was subsequently available for analysis.)

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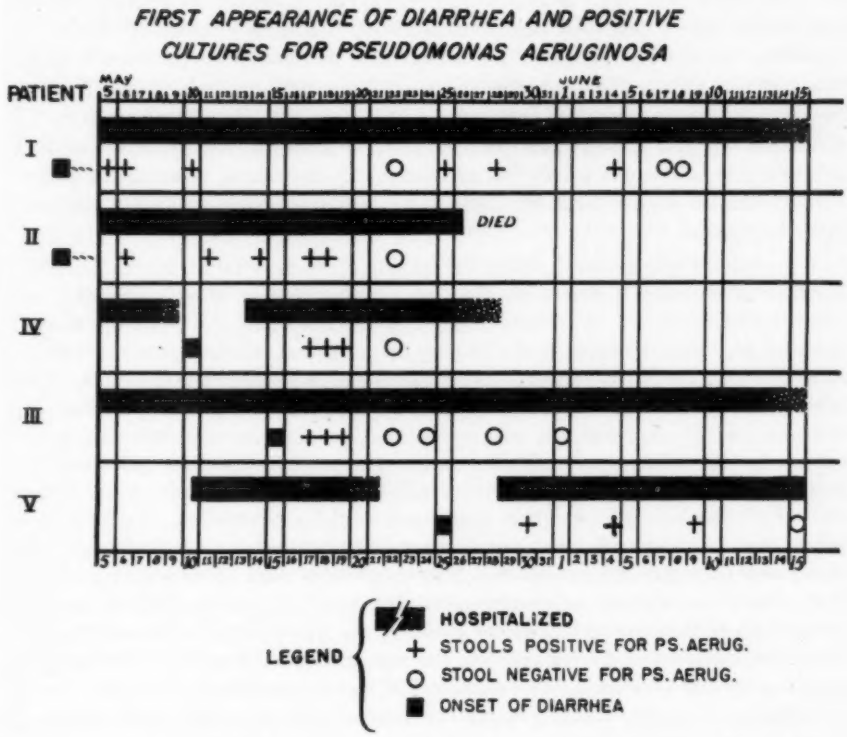


Fig. 1.—First appearance of diarrhea and positive cultures for *Pseudomonas aeruginosa*.

## CLINICAL PICTURE AND THERAPY EMPLOYED

The picture presented by the five patients studied most intensively was that of relatively mild enteritis. Clinically one would not have suspected *Ps. aeruginosa* as the etiological agent.

Patient I was a 17-week-old boy admitted to the Mount Sinai Hospital on March 22, 1948, because of a respiratory infection and aphthous stomatitis. He was treated with sulfadiazine and penicillin. Just before discharge he developed otitis media and diarrhea. At that time, only *Escherichia coli* was cultured from the stools. The diarrhea, while not severe, responded poorly to changes in formula and to administration of sulfadiazine and penicillin. On May 4, the forty-third hospital day, and the sixth day of diarrhea, he had six large, loose, watery, green stools. On that day he lost one pound in body weight. The following day the stools were positive for hemoglobin by the guaiac test and culture revealed *Esch. coli* and *Ps. aeruginosa*. A period of oral starvation followed by feeding of a dilute evaporated milk formula did not influence the character of the stools and the patient continued to have three to five loose

bowel movements a day. Streptomycin was given by mouth for 2 days (25 mg. four times daily) and then supplemented with this same amount by the intramuscular route. The strain of *Ps. aeruginosa* obtained from the child's stools was sensitive in vitro to 4 μg of streptomycin per milliliter (which was 20 times as resistant as the standard organism). This medication was continued for 11 days. At the end of this time the diarrhea had subsided, but the stool cultures continued to be positive for *Ps. aeruginosa* for 12 more days. During the period of diarrhea the white blood cell count ranged between 5,850 and 8,650 cells per cubic millimeter.

Patient II was a 7-week-old girl admitted to the hospital on March 31, 1948, because of diarrhea. From the time of admission until May 5, she had had several exacerbations. On May 5, the thirty-fifth hospital day, in spite of continuous penicillin therapy since the day of admission, the temperature rose to 102° F., and the child had symptoms of an upper-respiratory infection. The white blood count was 13,600 cells per cubic millimeter. The stools on this day were yellow, watery, stippled with green and red flecks, and positive for hemoglobin by the guaiac test. Stool culture was positive for *Esch. coli* and *Ps. aeruginosa*. The latter organism was repeatedly cultured from the stools during the next two-week period. The diarrhea gradually subsided during this time. Since the organism was reported to be sensitive in vitro to sulfadiazine, this drug was administered in doses of 0.10 Gm. every four hours starting on the forty-ninth hospital day. Nevertheless, 6 days later, the patient suffered another exacerbation of diarrhea. A single stool culture taken at this time was positive only for *Esch. coli*. Unfortunately, she succumbed before other stool cultures could be obtained. Post mortem examination was not permitted.

Patient III was a 2-month-old boy admitted to the hospital on April 28, 1948, because of congenital syphilis. He was treated with large doses of penicillin. As already noted, he was on the ward at the same time as several other children with diarrhea associated with *Ps. aeruginosa*. On May 17, the day the course of penicillin was completed, the patient had several loose stools, became dehydrated, and during the next twenty-four hours lost 9 ounces in weight. The nasopharyngeal and stool cultures were positive for *Ps. aeruginosa*. Two days later, on May 19, sulfadiazine was started (0.10 Gm. was given by mouth every four hours). This medication was discontinued after 4 days because it appeared to have no effect on the diarrhea which continued for 5 more days. However, the stool cultures taken after May 19 were positive only for *Esch. coli*. The white blood cell count during the period of diarrhea ranged between 5,500 and 8,500 cells per cubic millimeter.

Patient IV was a 5-month-old boy admitted to the hospital for the second time on May 14, 1948. He had been discharged 5 days earlier after recovering from bronchopneumonia. At the time of discharge several patients on the ward had diarrhea associated with *Ps. aeruginosa*. He had been well for two days at home. He then developed diarrhea and gradually became dehydrated. On admission his white blood count was 4,900 cells per cubic millimeter with a moderate shift to the left. Stool culture taken on admission was positive for

*Esch. coli.* However, another culture taken on the fourth hospital day was positive for *Ps. aeruginosa.* Cultures taken on the fifth and sixth hospital day were also positive. On admission the patient was given 10,000 units of penicillin intramuscularly every three hours. This had no effect on the course of the diarrhea. During the first 5 days in the hospital he had six to ten watery stools daily. Gradually by the eighth hospital day the number of stools diminished and their quality improved. Stool culture taken on the eleventh day was positive only for *Esch. coli.* It is believed that this patient was infected with *Ps. aeruginosa* during his first hospital admission. Supporting evidence for this belief is obtained from the serologic studies which will be presented.

Patient V was a 9-month-old girl also admitted to the hospital for the second time on May 29, 1948, because of diarrhea. Her first admission was from May 11, 1948, to May 21, 1948, because of right-upper lobe bronchopneumonia. This was treated with penicillin. During her first admission several children on the ward had diarrhea associated with *Ps. aeruginosa.* She had been well at home for four days after discharge, but on May 25, four days before admission she had four loose stools, began to vomit, and her temperature rose to 101° F. These symptoms increased during the next 4 days and she was readmitted to the hospital. On admission she was acutely ill, severely dehydrated, apathetic, and in shock. Her weight was 18 pounds, 12 ounces. Physical examination was otherwise negative. The white blood cell count was 4,200 cells per cubic millimeter with 39 per cent polymorphonuclear leucocytes, 7 per cent nonsegmented leucocytes, 50 per cent lymphocytes, and 4 per cent monocytes. The hemoglobin was 11.3 Gm. The blood carbon dioxide combining power was 23 volumes per cent. Stool culture was positive for *Ps. aeruginosa.* Oral feedings were stopped and a regimen similar to that outlined by Karelitz[4] was instituted. A continuous intravenous infusion was started and through this she received ⅙ molar lactate solution, normal saline, plasma, and blood. Oral feedings were resumed thirty-six hours after admission with a diluted evaporated milk formula. For the next 5 days stools continued to be watery and the formula was not increased. On June 4, the seventh hospital day, another thirty-six-hour period of oral starvation was started. Although the stools did not improve during this period, oral feedings were cautiously resumed. Hydration was maintained by continuous intravenous infusion. From the seventh to the fourteenth hospital day the patient had an average of six loose, watery, green stools daily. Five of the six stool cultures taken during the first two weeks of hospitalization were positive for *Ps. aeruginosa.* During this time the patient was on continuous penicillin therapy. On June 11, the fifteenth hospital day, she was given 18 mg. of Polymyxin B every four hours by mouth (i.e., 2 mg. per kilogram of body weight). The drug was started in the afternoon, and on this day the patient had two small loose stools. During the previous day she had had six loose stools. Within twenty-four hours after the start of polymyxin therapy the patient's stools were of better quality. The child took her formula better and the amount of oral feeding was thereafter increased rapidly. By the fourth day after the institution of treatment with Polymyxin B she was taking full fluid requirement by mouth. Stool cultures

obtained 4 days after the start of polymyxin therapy were negative for *Ps. aeruginosa*, as were those taken subsequently. The antibiotic was continued for 6 days and the patient was discharged on the twenty-sixth hospital day.

Thus far, attempts to treat infections due to *Ps. aeruginosa* with antibiotics have been ineffectual.[5] The results with polymyxin in Patient V and the recent report of in vitro studies with this drug by Alexander, Leidy, and Redman[6] suggest that it deserves further attention. However, the oral route should be used, as it was here, to avoid high blood levels and subsequent renal damage.

## PROPHYLAXIS

The ease with which infections with *Ps. aeruginosa* may spread among hospitalized patients and the resistance of these infections to therapy, indicates that thought must be given to means of prophylaxis. Because of the suggestion in this outbreak that the organism was transmitted by hands or commonly used instruments, an attempt was made to test the bactericidal effect of several readily available cleaning agents upon *Ps. aeruginosa*. An ear speculum, a pair of forceps, and a rubber glove were dipped into a broth culture of *Ps. aeruginosa*, dried, and cultured. They were then left for two minutes in a freshly prepared 70 per cent alcohol solution, a common household detergent solution (Alconox) or a soapy water solution, dried on a paper towel and recultured. The results showed no detectable inhibition of growth by the detergent and soapy water solutions, but almost complete inhibition by the 70 per cent alcohol solution.

The fact that a pair of forceps used to handle nipples was presumably kept in 70 per cent alcohol solution and yet, as noted heretofore (under Epidemiology), was contaminated with *Ps. aeruginosa* emphasizes the need for care in ascertaining that alcohol solutions really contain the desired concentration.

## BACTERIOLOGY

The bacteriology of the Pseudomonas organisms is variable. Which of their many properties are the most significant for classification is not clear. Christie[7] found that ability to grow well at 37° C. and to hemolyze sheep red blood cells permitted him to differentiate the pathogenic from saprophytic strains. The tests selected for our study were the appearance of the growth on nutrient agar slants after twenty-four hours, motility, production of green pigment, fluorescence in ultraviolet light, hemolysis on human blood agar, liquefaction of gelatin within 14 days, and the coagulation of litmus milk.

As seen from Table I, these tests have been used to compare five strains of *Ps. aeruginosa* recovered from the stools of the five patients with diarrhea and one strain from the hands of one of the ward nurses, with six strains recovered from other sources during the next few weeks. It is apparent that none of these tests offers a clear means of differentiating between the strains isolated from the children with diarrhea and those obtained from the others.

## SEROLOGY

Antisera against several strains of *Ps. aeruginosa* were prepared in rabbits and agglutination tests were carried out with each of the strains listed in Table I.

TABLE I. BACTERIOLOGY OF STRAINS OF *Ps. aeruginosa*

| STRAIN | APPEARANCE ON AGAR SLANT AFTER 24 HOURS | GREEN PIGMENT | FLUORESCENCE IN ULTRAVIOLET LIGHT | HEMOLYSIS ON BLOOD AGAR | GELATIN LIQUEFACTION | COAGULATION OF LITMUS MILK | MOTILITY |
|---|---|---|---|---|---|---|---|
| *Diarrhea strains* | | | | | | | |
| I | Smooth | + | + | 0 | + | + | + |
| II | Smooth | + | + | + | 0 | + | + |
| III | Smooth | + | + | Slightly + | + | + | + |
| IV | Smooth | + | + | + | 0 | + | + |
| V | Smooth | + | + | + | + | + | + |
| Miss T. | Smooth | + | + | Slightly + | + | + | + |
| *Nondiarrhea strains* | | | | | | | |
| S | Smooth | + | 0 | + | + | + | + |
| VA | Smooth | + | + | 0 | 0 | 0 | + |
| A | Smooth | + | + | + | + | + | + |
| F | Mucoid | + | + | + | + | + | + |
| RL | Mucoid | + | + | + | + | 0 | + |
| N | Mucoid | + | + | + | + | + | + |

The antisera were of the anti-H or flagella type. They were prepared by giving rabbits a series of four intravenous injections of increasing amounts of an antigen at 3- to 4-day intervals. The antigens were prepared from eighteen-hour broth cultures and diluted with an equal volume of 0.6 per cent formalinized saline. The animals were bled 10 days later and if the titer of homologous agglutinin was not satisfactory, two further injections were given intra-abdominally. This was necessary with anti-I and anti-RL animals. The agglutination tests were carried out by mixing 0.2 ml. of varying dilutions of rabbit serum with 0.2 ml. of the antigen prepared from eighteen-hour cultures on agar slants, inactivated with 0.6 per cent formalinized saline, washed and made to approximate the turbidity of a McFarlane #3 standard. The mixtures were incubated at 56° C. for from 2 to 3 hours and at 4° C. overnight. They were then examined for macroscopic agglutination.

It is apparent from Table II that the *Ps. aeruginosa* organisms form a heterologous group consisting of at least four different serologic types. It is of interest to observe that the strains obtained from the patients with diarrhea fell into a single group excepting the strain from the first patient whose organism seems to be in a group of its own. The culture F which also reacted with the anti-V serum was obtained from the ear canal of an older child who was on another ward at the time of the diarrhea.

In order to determine whether the strains agglutinated by anti-V serum formed an homologous group an attempt was made to absorb the agglutinins with V, III, and RL organisms. Anti-V serum was diluted 1:10 with saline and mixed with an equal volume of a thick suspension in saline of fresh live cultures from an agar slant. The mixture was shaken, incubated at 56° C. for two hours and overnight at 4° C. The supernatant was removed after centrifugation and tested with the standard antigen as in Table II. The results are summarized in Table

TABLE II. SEROLOGY OF STRAINS OF *Ps. aeruginosa*

| STRAINS | NORMAL RABBIT SERUM | ANTI-I SERUM | ANTI-V SERUM | ANTI-RL SERUM |
|---|---|---|---|---|
| *Diarrhea strains* | | | | |
| I | 0* | 640† | 0 | 0 |
| II | 0 | 0 | 160 | 0 |
| III | 0 | 0 | 160 | 0 |
| IV | 0 | 0 | 320 | 0 |
| V | 0 | 0 | 160 | 0 |
| Miss T. | 0 | 0 | 160 | 0 |
| *Nondiarrhea strains* | | | | |
| S | 0 | 0 | 0 | 320 |
| VA | 0 | 0 | 0 | 0 |
| A | 0 | 0 | 0 | 0 |
| F | 0 | 0 | 160 | 0 |
| RL | 0 | 0 | 0 | 80 |
| N | 0 | 0 | 0 | 5120 |

*1-40 was lowest dilution tested.
†Reciprocal of highest dilution giving definite agglutination.

TABLE III. ABSORPTION OF ANTI-V AGGLUTININ

| ANTI-V SERUM | TESTED AGAINST STRAIN: | TITER |
|---|---|---|
| Not absorbed | V | 80* |
| | III | 160 |
| Absorbed with V | V | 0† |
| | III | 0 |
| Absorbed with III | V | 0 |
| | III | 0 |
| Absorbed with RL | V | 80 |
| | III | 160 |

*Reciprocal of highest dilution giving definite agglutination.
†1-40 was lowest dilution tested.

III. Although by the nature of this experiment, heat-labile heterologous agglutinins might have been undetected even if present, both V and III bacterial suspensions completely absorbed the agglutinins from the anti-V serum, while the RL strain did not reduce its titer.

The serologic heterogeneity of the *Ps. aeruginosa* strains has been observed by various workers. Most recently Munoz, Scherago, and Weaver[8] reported that there were at least two distinct groups, one of which was homogeneous and the other heterogeneous. Our studies indicate that there may be at least four such groups. It is significant that four of the five cases of diarrhea yielded organisms which were serologically identical.

It was possible to test sera from three of the patients during their convalescence for the development of agglutinins to their own organism. As is shown in Table IV none were found to have such agglutinins. Contrariwise two of nine adult sera taken at random and tested against the I strain were found to have agglutinins in a titer of 1:160 and 1:320. These findings are reminiscent of reports concerning infection with Shigella.

Watt and De Capito[9] in a study of the development of agglutinins against *Shigella paradysenteriae* in forty-five patients concluded that the agglutination test did not provide a reliable means of diagnosing past infection. Although individuals found to have positive stool cultures had a definite tendency to have

higher agglutinin titers, these were neither consistent nor high enough to permit interpretation of individual results. Persons with a negative agglutination test were just as likely to have positive stool cultures as those with demonstrable agglutinins, and there was no apparent relation between the titer level and the presence of clinical signs of infection.

About twenty years ago Lilley and Bearup[10] studied an outbreak of generalized infections caused by *Ps. aeruginosa* in adults. They found significant rises in agglutinin titer for this organism in many of their patients. A possible explanation for our failure to obtain similar results may be that we studied only infants with relatively mild infections which were limited to the gastrointestinal tract.

TABLE IV. EXAMINATION OF PATIENT'S SERA FOR *Pseudomonas aeruginosa* AGGLUTININS

| PATIENT | DATE OF SERUM | DAYS AFTER ONSET OF ILLNESS | ANTIGEN | TITER |
|---|---|---|---|---|
| I | 6- 2-48 | 33 | I | 0 |
| | 6-10-48 | 41 | I | 0 |
| | 6-21-48 | 52 | I | 0 |
| III | 6- 2-48 | 17 | III | 0 |
| | 6-10-48 | 25 | III | 0 |
| V | 6-21-48 | 27 | V | 0 |

## SUMMARY

1. A small, relatively mild outbreak of diarrhea associated with *Pseudomonas aeruginosa (Bacillus pyocyaneus)* occurring on an infants' ward is described.

2. The clinical course of five patients is given together with an account of the therapy employed. On the basis of encouraging results in one patient and reports of in vitro sensitivity of the organism, it is suggested that when other forms of chemotherapy fail, Polymyxin B be tried by the oral route.

3. It is shown that washing a contaminated object in soap and water does not reduce the *Ps. aeruginosa* count, while soaking in 70 per cent ethyl alcohol for 2 minutes is effective. It is recommended that this procedure be included in the hospital technic for prevention of cross infections.

4. Among twelve strains of *Ps. aeruginosa* studied for flagella antigens there were at least four serologic groups. The strains recovered from four of the five patients with diarrhea were serologically homologous and identical with the strain recovered from the hands of one of the nurses. The sole exception was the first patient whose organism was in a serologic group of its own.

5. The sera of convalescing infants did not contain agglutinins for their homologous organism. Nevertheless some adult sera taken at random had agglutinins in moderately high titer for one of the strains associated with the diarrhea.

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# OTITIS MEDIA IN INFANCY: TREATMENT WITH STREPTOMYCIN

## Report of Five Cases Caused By Pseudomonas Aeruginosa (Bacillus Pyocyaneus)

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MANY agents have been used in treating infections caused by *Pseudomonas aeruginosa*. Vaccines as used by Berger[1] and Gracey[2] are of questionable value. Antiserums as suggested and experimentally studied by Barker,[3] Garretson and Cosgrove,[4] and Ford[5] have some value in animals, but this therapy has not been used widely in humans.

Nearly all antiseptics have been employed against this microorganism. Probably the most effective is parachlorphenol, as reported by Meleney, Johnson, Pulaski, and Colonna.[6] These authors studied its activity in vitro and in vivo and obtained excellent results in the treatment of osteomyelitis and superficial ulcerations of this origin. An anterior mediastinal infection, caused by *Ps. aeruginosa*, complicating a dermoid cyst which had been present nine months, disappeared quickly and completely after the use of parachlorphenol, according to Robitzek and Prausnitz.[7]

Bartlett and Poe[8] studied the effect of ultraviolet light on this microorganism and concluded that it is more resistant to this agent than the colon bacillus, possibly because pigment produced by *Ps. aeruginosa* impedes penetration of the rays. Stein[9] reported success with the use of ultraviolet light in a severe skin infection caused by this bacillus.

The effectiveness of the sulfonamide drugs against *Ps. aeruginosa* has caused considerable controversy. Joy's studies in vitro indicated a suppressive effect on some strains.[10] Experimental studies on mice by Cooper, Gross, and Lewis[11] gave no evidence of protection by these drugs. Helmholz,[12] on the other hand, reported sulfanilamide administered orally to humans capable of killing several strains of *Ps. aeruginosa* causing infection of the urinary tract. Long and Bliss[13] also found this drug useful. To condense opinions from many sources, it appears that a few strains are moderately susceptible to sulfonamides, a considerable number slightly susceptible, and a great number nonsusceptible.

Early in the history of penicillin therapy, Hobby, Meyer, and Chaffee,[14] and Keefer, Herwick, Van Winkle, and Putnam[15] reported that experimentally this agent is ineffective against *Ps. aeruginosa*, as it is against most gram-negative organisms. The studies of Long and his associates,[16] and Collins, Paine, and Finland[17] indicate that aureomycin is also ineffective against this bacillus. The effectivity of Chloromycetin has not been determined, although according to Buckman[18] it has been effective in a few cases of urinary infection caused by this microorganism.

Although less effective against all strains of *Ps. aeruginosa* than against other common gram-negative organisms such as *Escherichia coli, Proteus vul-*

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*garis,* and *Aerobacter aerogenes,* streptomycin has been, for several years, the most effective weapon available against these microorganisms. The studies of Waksman, Bugie, and Schatz,[19] Buggs, Bronstein, Hirshfeld, and Pilling,[20] and Carroll, Allen, and Doubly,[21] to name but a few, attest to its efficacy. Helmholz[22] reported streptomycin more effective than the sulfonamides against gram-negative bacilli. His data indicate that concentrations of 100 u. of streptomycin per c.c. destroy *Ps. aeruginosa* in twenty-four hours and that concentrations of 1,330 u. kill all of these microoganisms in three hours, most of them in one hour.

In the five cases reported here, two of the infants were under 2 weeks of age, and none was over 5 months of age. All had purulent otitis media caused by *Ps. aeruginosa,* an organism that is usually a saprophyte. In each case the infant had been delivered at St. Vincent's Hospital; the patient in Case 1 received treatment for the infection prior to dismissal, two patients were readmitted for treatment, and two were not hospitalized.

### CASE REPORTS

CASE 1.—B., a girl, was delivered on May 19, 1947, after an uneventful pregnancy and labor. She was the third child and weighed 3.122 kg. She was bottle fed and appeared normal until pus was noted in the left ear when she was having her morning bath on the fifth day of life. There was no fever, nor evidence of infection of the respiratory tract. Examination of the blood showed Hb 15.9 Gm. per 100 c.c., red blood count 4.9 million per cubic millimeter and white blood count 13.1 thousand per cubic millimeter with neutrophiles 39 per cent, and lymphocytes 61 per cent. Culture of the thick, yellow discharge showed *Ps. aeruginosa.*

The infant was transferred to the pediatric ward. Three days later, there was nasal congestion, and a thick, yellow discharge from the other ear was noted. When she was 15 days of age, there was a moderate yellow discharge from the vagina. Cultures of the discharge from this site and from the nose and ears were positive for *Ps. aeruginosa.*

*Course and Treatment.*—The day that the discharge from the ear was discovered, administration of 5,000 u. of penicillin every 3 hours was begun. Three days later the dose was doubled. Beginning on the following day, 0.22 Gm. of sulfadiazine per kilogram body weight was given every twenty-four hours for 4 days. There was no improvement. On June 4, 9 days after the original infection was noted, 41 mg. of streptomycin (about 80 mg. per kilogram body weight in twenty-four hours) was given intramuscularly every 4 hours and was continued for 3 days. At the end of this period all discharge had disappeared from the ears, nose, and vagina, and the next day the patient was discharged from the hospital. Subsequent observation revealed no further difficulty. There was elevation of temperature (maximum 39° C. [102° F.] by rectum) for 2 days only, prior to the administration of streptomycin. The infant gained 0.5 kg. while in the hospital.

CASE 2.—L. A. B., a girl, was delivered on Oct. 9, 1947, and weighed 3.175 kg. at birth. She was well and had normal weight and height increments until December 15, when she was 10 weeks old. At that time the mother noted a yellowish discharge from the left ear. There had been no infection of the upper part of the respiratory tract, nor evidence of pain. Culture was positive for *Ps. aeruginosa.* Sulfadiazine, 0.132 Gm. per kilogram body weight in twenty-four hours with double initial dose, was prescribed. Four days later the discharge continued unchanged. The patient was then admitted to the hospital.

Urinalysis gave normal results. Examination of the blood revealed Hb 9.9 Gm. per 100 c.c., red blood count 3.3 million per cubic millimeter and white blood count 12.2 thousand per cubic millimeter with neutrophiles 24 per cent, juveniles 4 per cent, segmented forms 20 per cent, eosinophiles 1 per cent, basophiles 1 per cent, monocytes 1 per cent, and lymphocytes 73 per cent.

*Course and Treatment.*—Four 50 c.c. blood transfusions were given on successive days. Treatment with streptomycin, 50 mg. every four hours (about 60 mg. per kilogram body weight in twenty-four hours) was started on admission and continued for 6 days. At the end of this period there was no drainage from the ear, and the patient was discharged from the hospital the following day. At no time did she have fever and she gained 170 Gm. while in the hospital. She experienced no further difficulty.

CASE 3.—J. C., a normal girl weighing 3.77 kg., was delivered on Nov. 30, 1947. She was well until the thirteenth day of life when stomatitis developed and she took her bottle poorly. The mother thought she had fever two nights later, and examination the following morning revealed a thick, yellow discharge in the external canal of the right ear. In addition, there were present a hyperemic tongue with raw, slick margins and two ulcers about 1 cm. in diameter on the floor of the mouth. The nose was moderately congested and had a mucous discharge. There was no elevation of temperature. She was admitted to the hospital, and a specimen for culture was taken from the ear. Urinalysis gave negative results. Examination of the blood showed Hb 16.3 Gm. per 100 c.c., red blood count 5.1 million per cubic millimeter, and white blood count 12.6 thousand per cubic millimeter with neutrophiles 34 per cent, eosinophiles 2 per cent and lymphocytes 64 per cent.

*Course and Treatment.*—Penicillin, 10,000 u. every three hours and sulfadiazine, 0.22 Gm. per kilogram body weight in twenty-four hours with double initial dose, were prescribed. On the fourth hospital day the culture was reported positive for *Ps. aeruginosa.* The in vitro sensitivity test (Buggs' method[20]) showed that the microorganism was sensitive to streptomycin. There had been no improvement in the otitis. Treatment with streptomycin, 41 mg. every four hours (about 60 mg. per kilogram body weight in twenty-four hours), was then started, and the penicillin was discontinued. Two days later the sulfadiazine was discontinued. The ear showed improvement, but did not remain dry for an entire twenty-four hour period; so 7 days after streptomycin therapy was begun, the dosage was doubled. Three days later, evidence of aural infection had disappeared, and the following day the infant was discharged from the hospital. During the period of hospitalization she had no fever and gained 85 Gm. There was no further difficulty.

CASE 4.—P. McC., a girl, weighed 3.402 kg. at birth on May 17, 1948, and developed normally until the age of 20 weeks, when a thick, yellow discharge from the left ear was noted. She had no fever and no respiratory infection. She ate and slept well. Examination revealed no abnormalities except the discharge. A specimen for culture was taken.

*Course and Treatment.*—She was given 150,000 u. of penicillin in oil, and a triple sulfonamide preparation, about 0.22 Gm. per kilogram body weight in twenty-four hours with double initial dose, was prescribed. Three days later the culture was positive for *Ps. aeruginosa.* Previous therapy was stopped, and 75 mg. of streptomycin every four hours (about 58 mg. per kilogram body weight in twenty-four hours) was started. At the end of 6 days there was no discharge, and the streptomycin was discontinued. At no time was the temperature elevated. There was no recurrence.

CASE 5.—D. J. McI., a girl 12 weeks of age, had developed normally since birth on Nov. 25, 1948, and had been well except for an infection of the upper

part of the respiratory tract at 2 weeks of age, from which she had fully recovered. When she was examined on Feb. 23, 1949, there was a profuse thick, yellowish-green discharge from the left ear that had been present for 3 days. She had been regurgitating more than usual for 5 days. There had been no discernible fever. She had seemed restless, but not ill. Examination of the blood showed Hb 10 Gm. per 100 c.c., red blood count 3.4 million per cubic millimeter, and white blood count 4.25 thousand per cubic millimeter, with neutrophiles 31 per cent, lymphocytes 65 per cent, monocytes 1 per cent, and eosinophiles 3 per cent. A specimen of the secretion from the ear was taken for culture.

*Course and Treatment.*—A mixture of sulfadiazine and sulfamerazine, 0.132 Gm. per kilogram body weight in twenty-four hours with double initial dose, was ordered, and 200,000 u. of penicillin procaine in oil was given intramuscularly. Two days later, on February 25, the discharge was still present. There had been no fever. The infant had been restless, but ate well. The culture was positive for *Ps. aeruginosa*. Streptomycin, 50 mg. intramuscularly every four hours (about 50 mg. per kilogram body weight in twenty-four hours), was started, and the sulfonamides were discontinued. Three days later there was still some discharge present, though it was much less thick. There had been an elevation of temperature on one occasion to 38.33° C. (101° F.) by rectum. On the fifth day of treatment with streptomycin, there was no discharge. Not until this time did a sensitivity test (Buggs' method[20]) show that the strain of *Ps. aeruginosa* causing the infection was poorly sensitive to streptomycin. The treatment was discontinued, and the trouble did not recur.

## DISCUSSION

The probability that the cases reported were cases of primary infection caused by *Ps. aeruginosa* rests on (1) the nature of the pus, which was thick, greenish-yellow in color and musty in odor, (2) the fact that the infants did not seem ill, and (3) bacteriologic evidence. While the original infection may have been a "silent" one caused by other organisms, by the time pus was discovered it was the infection caused by *Ps. aeruginosa* that required treatment.

Despite the fact that the anatomy of the ear in the young peculiarly invites infection and, as Leroux[23] suggested, latent otitis media is perhaps the rule in every neonatal infant, purulent discharge from the ear is rarely observed in the newborn nursery. Dolan and Grand[24] noted its occurrence in only one case in a survey of the records of over 8,000 newborn babies. Of 11,503 live births at St. Vincent's Hospital, Jacksonville, Fla., from January, 1945, through June, 1949, otitis media was observed in but one of the newborn infants (Case 1).

In two of the five cases of this series there were no discoverable predisposing factors for otitis media. In Case 1, the infant had a spreading infection involving both ears, the nose, and the vagina, as well as fever for 2 days, and may have had sepsis. There was present in Case 3 an infection of the upper part of the respiratory tract, and in Case 5 more regurgitation than usual had occurred for 2 days before the aural discharge was noted. All five infants were delivered in the same hospital and were in the same nursery. While it might be possible to harbor bacteria of such low virulence as *Ps. aeruginosa* for long periods of time, it is not likely that dormancy of a pathogen would have occurred for 10, 12, or 20 weeks (Cases 2, 4, and 5). No attempt was made to study the bacterial flora of the respiratory tracts of the hospital personnel.

The low virulence of *Ps. aeruginosa* in general, and in these cases in particular, is illustrated by the fact that fever was present in only three of the five cases and in no case longer than for 2 days (Table I). In Case 1 the maximal temperature was 39° C. (102° F.) by rectum, in Case 3 it was not recorded, and in Case 5 the highest recorded temperature was 38.33° C. (101° F.) by rectum. The infants did not appear ill, and nutrition was not affected. These findings are in sharp contrast to those in the four cases of otitis media in newborn infants reported by Parsell,[25] in all of which the infants had fever and were acutely ill. The bacterial etiology was not determined in these cases, but the discharge was serous in character.

TABLE I. ANALYSIS OF FIVE CASES OF PURULENT OTITIS MEDIA CAUSED BY PSEUDOMONAS AERUGINOSA

| CASE NO. | AGE | INDIRECT CAUSE | FEVER | TREATMENT* | | | NO. DAYS DRAINAGE BEFORE STREPTOMYCIN | NO. DAYS DRAINAGE AFTER STREPTOMYCIN |
|---|---|---|---|---|---|---|---|---|
| | | | | SULFONAMIDES | PENICILLIN | STREPTOMYCIN | | |
| 1 | 5 days | Sepsis(?) | 2 days 39° C. (102° F.) Maximum | 4 days N.B. | N.B. | 80 mg./kg. 3 days | 9 | 4 |
| 2 | 10 weeks | | None | 4 days N.B. | None given | 60 mg./kg. 6 days | 4 | 6 |
| 3 | 15 days | Upper-respiratory infection | 2 days Maximum? | 6 days N.B. | N.B. | 60 mg./kg. 10 days | 4 | 10 |
| 4 | 20 weeks | | None | 3 days N.B. | N.B. | 58 mg./kg. 6 days | 3 | 6 |
| 5 | 12 weeks | Vomiting(?) | 1 day 38.33° C. (101° F.) Maximum | 2 days N.B. | N.B. | 50 mg./kg. 5 days | 5 | 5 |

*N.B. = no benefit;

The use of streptomycin, a toxic drug with the ability to cause permanent damage to the eighth cranial nerve, in the treatment of an infection caused by an agent of such low virulence may be questioned. The danger to the very young of infection, whatever the site, with septicemia, meningitis, or other dire complications is well known. The age of the patients was the principal reason for using the drug. According to recent dosage schedules as used by Riggins and Hinshaw[26] and most other authors, the doses given these infants were high. In the administration of streptomycin three- and four-hour intervals are now being abandoned for six- or eight-hour intervals. These infants were treated with streptomycin for an average of 6.2 days, however, and in no case was treatment continued longer than 10 days. Lincoln, Kirmse, and De Vito,[27] who have had extensive experience with the drug, have observed toxic manifestations as early as the second day of treatment, but have noted little permanent effect, even when this drug is given for many weeks in the treatment of tuberculous meningitis. They give infants with tuberculous meningitis 0.5 to 1.0 Gm. in twenty-four hours regardless of weight. Nevertheless, in the light of present experience, much smaller doses should be used unless the prognosis in the disease being treated is extremely grave.

Ideally, sensitivity tests to all bacteria, especially to *Ps. aeruginosa* with its numerous strain variations, should be made before employing streptomycin. In Case 3 the strain proved susceptible to therapeutic amounts of streptomycin and in Case 5 it did not. In other cases tests were not made. It is possible that in all of these cases recovery without complications would have occurred even if no treatment had been given. Unless susceptibility tests are a routine laboratory procedure, the average laboratory will often return reports after treatment is completed. Tests in which antibiotic impregnated filter papers are employed will usually give rapid and satisfactory results, though they are less accurate than Buggs' method[20] and similar methods.

No local treatment was used in this series, other than removal of visible pus with cotton swabs. In each case, the perforation of the drum seemed adequate for free drainage.

## SUMMARY

Five cases are reported in which purulent otitis media developed in infants under 20 weeks of age, one of whom was 5 days old. In each case, culture was positive for *Pseudomonas aeruginosa*. The infants were treated with sulfonamides and penicillin without benefit. After parenteral administration of streptomycin, recovery took place in from 4 to 10 days, but was not necessarily due to this drug. The principal reason for using streptomycin was the extremely early age of the patients.

Appreciation is expressed to Mildred M. Galton, M.S., bacteriologist of the Florida State Board of Health, for confirmatory bacteriologic work and sensitivity tests.

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# ACUTE PULMONARY INTERSTITIAL AND MEDIASTINAL EMPHYSEMA (AIRBLOCK) AND PNEUMOTHORAX IN INFANCY AND EARLY CHILDHOOD

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DURING acute and chronic disease of the respiratory tract, or states of excessive strain on the pulmonary apparatus, or following trauma, air may suddenly escape under pressure from the alveolar structures into the interstitial tissues of the lungs, the mediastinum, their fascial extensions, and the pleural spaces. The mechanism leading to the production of the resulting pulmonary interstitial and mediastinal emphysema, or airblock, and of pneumothorax has been described by Hamman[1, 2] and by the Macklins.[3, 4]

The condition may develop unsuspectedly in infants and children, and may be exhibited clinically only by persistent dyspnea and cyanosis of a severity not accounted for by physical signs on examination. Roentgenography of the chest may provide the initial clue to the presence of extravasations of air that underlie the acute respiratory and circulatory embarrassment.

To illustrate this sequence of events and to demonstrate some representative causes of airblock, the following case histories are presented.

## CASE REPORTS

CASE 1.—On March 29, 1949, E. A., a 3½-month-old Puerto Rican female infant, weighing 4,763 grams, was admitted to the hospital for cyanosis and marked dyspnea. The baby had been well until 2 days before admission, when vomiting developed. The next day vomiting and retching became incessant. The infant appeared in pain and cried between bouts of emesis. Early the next morning, respiratory difficulty and tachypnea were noted. The baby was brought to the hospital that afternoon.

Physical examination revealed a moribund infant, with a temperature of 37.2° C., slight dehydration, and an ashen-gray color. Respirations were 70 per minute and labored. Ears, eyes, nose, and throat were normal. Percussion showed impaired resonance over the upper-right chest, anteriorly and posteriorly. Breath sounds were diminished. No râles were heard. Heart sounds were normal. Abdomen was soft and not tender; no masses were palpable. The infant was immediately placed under an oxygen hood. Color improved, but dyspnea persisted. Fluids were given by hypodermoclysis; penicillin was administered.

Blood count showed 3,560,000 red cells and a hemoglobin of 62 per cent. White cells were 11,800, with 88 per cent neutrophiles, 11 per cent lymphocytes, and 1 per cent mononuclears. Sedimentation rate was 6 mm. in one hour. Carbon dioxide combining power of the blood was 46 volumes per cent. Urine had a specific gravity of 1.020 and a pH 4.5, and gave negative reactions to albumin and glucose tests.

Because of the grave condition of the baby, roentgenographic examination was deferred until the following morning. Posteroanterior view of the chest showed a normal cardiac silhouette. No shifting of the mediastinum was noted (Fig. 1). The upper mediastinum and heart borders were delineated by lines of decreased density which gave an H-shaped appearance. In addition, bilateral pneumothorax was seen in the lower lateral areas of the pulmonary fields. Right lateral view of the chest disclosed air in anterior superior mediastinum (Fig. 2).

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On the third hospital day, examination of the chest showed only distant heart sounds. Temperature was normal. There was moderate dyspnea even with oxygen; but color was good. Respiratory rate varied between 40 and 65 per minute. Since dyspnea persisted, mediastinal aspiration was attempted. A 25-gauge needle was inserted into the anterior mediastinum just above the suprasternal notch, and connected to a water manometer attached to the needle by a three-way stopcock. First puncture revealed a negative pressure, and the second a pressure of 4 cm. of water. Only 1 cubic centimeter of air could be aspirated from this area. No further attempts at aspiration were made.

By the fifth hospital day, dyspnea and respiratory distress subsided when the infant was in oxygen. Roentgenographically, a small left-sided pneumothorax was still visible, but the mediastinal emphysema was no longer present. By the eighth day the baby showed no dyspnea or cyanosis when removed from oxygen; respiratory rate was 26 per minute. On the tenth hospital day the clinical course was complicated by varicella. The baby was transferred temporarily to a contagious disease hospital.

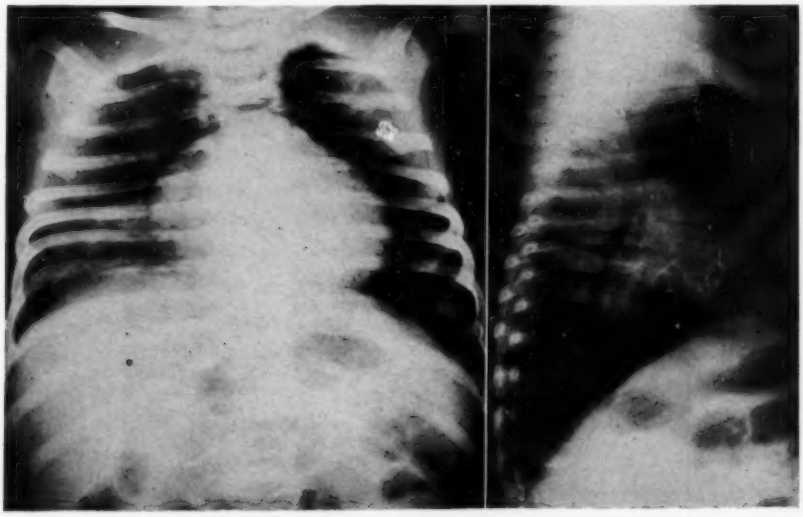

Fig. 1. Fig. 2.

Fig. 1.—Posteroanterior view of the chest showing mediastinal emphysema and bilateral pneumothorax (Case 1).

Fig. 2.—Lateral view of the chest showing anterior mediastinal emphysema (Case 1).

Five days later she was readmitted. Roentgenograms now revealed complete absorption of the air from the mediastinum and the thorax, fifteen days after onset of illness. The baby was observed for another month. Further roentgenograms showed no recurrence of the mediastinal emphysema or the pneumothorax. The cause of the airblock could not be determined with certainty, but in the absence of demonstrable infection, it may have been precipitated by the violent bouts of vomiting and retching experienced by the infant.

CASE 2.—On May 15, 1949, M. L., a one-month-old white male infant weighing 2,807 grams, a private patient of Dr. Paul Freud, was admitted to the hospital for restlessness and inability to suck. Birth was premature and complicated by irregularity and slowing of the fetal heart rate during the first stage of labor. Delivery was successfully completed. Respirations were spontaneous. Birth weight was 1,843 grams. The baby did well and was discharged on the tenth postnatal day with a weight of 2,381 grams.

Progress continued satisfactorily until the baby was 2½ weeks of age, when sucking became very poor. Feedings were given by teaspoon. Excessive crying and restlessness were

present. There was no vomiting at this time. Hoarseness, but no cough, was noted three days prior to admission. On arrival at the hospital, examination showed a dehydrated and poorly nourished infant, with gray color, who weighed 2,807 grams. Temperature was normal. Tissue turgor was poor. Cry was hoarse and respirations rapid. There was cyanosis. Generalized adenopathy, an umbilical hernia, and a right hydrocele were present. Neurological examination showed nothing of significance. Heart was normal and lungs appeared clear.

Blood count showed 5,800,000 red cells and a hemoglobin of 116 per cent. White cells were 29,300, of which 40 per cent were polymorphonuclears, 13 per cent eosinophiles, 41 per cent lymphocytes, 3 per cent basophiles, and 3 per cent mononuclears. Subsequent blood count gave a normal percentage of eosinophiles. Urine was negative. Nonprotein nitrogen of the blood was 41.9 mg. per cent; carbon dioxide combining power determination was 23 volumes per cent. Roentgenograms of the chest on the day after admission showed a mottled infiltration of the inner two-thirds of both lung fields. A clinical diagnosis was made of aspiration pneumonia.

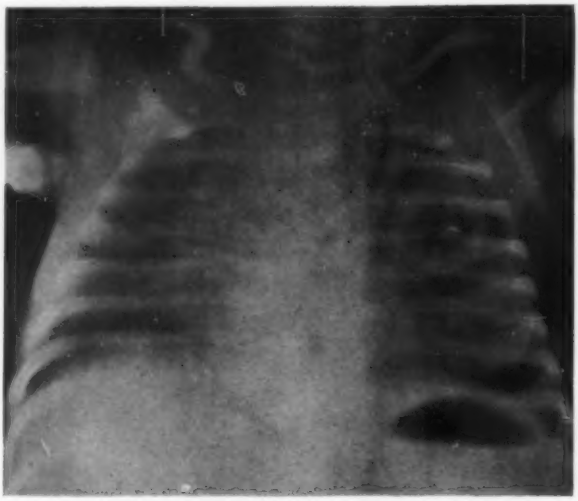

Fig. 3.—Anteroposterior view of the chest showing left pneumothorax (Case 2).

Immediate therapy was directed toward combatting infection, restoring hydration, and overcoming acidosis. Parenteral penicillin and streptomycin were given, as well as hypodermoclyses of normal saline and sodium lactate solutions. A formula was offered of diluted evaporated milk with Dextri-Maltose.

Clinical Course: At first, the baby vomited almost every feeding. The formula was changed to a powdered milk preparation which was better tolerated with cessation of regurgitation. In spite of daily parenteral fluids, the carbon dioxide combining power of the blood remained persistently low until May 30, when it rose to 35.7 volumes per cent. No further determinations were made because of poor veins and the necessity of withdrawing blood daily by puncture either of right or left internal jugular veins. Clinical course was afebrile.

Roentgenograms of the chest were repeated on May 20, five days after admission, and showed clearing of both pulmonary fields. Surprisingly enough, another film taken three days later, showed a pneumothorax at the left base (Fig. 3). The subsequent course of events was favorable. The rapid respirations subsided, cyanosis disappeared, and color improved. The pneumothorax was absorbed 6 days after first detection roentgenologically. The baby's general condition improved and its weight rose to 5,642 grams at the time of discharge on June 18, 1949. The cause of the pneumothorax could not be determined with certainty. Factors which may have contributed are those of the vomiting, the pneumonia,

and possibly the daily venipunctures of the internal jugular veins, a procedure not without its attendant risks. In this connection, Goldstein[5] recently reported on the occurrence of accidental fatal perforation of the trachea during venipuncture of the internal jugular veins of two infants of the ages 7 and 9 days.

CASE 3.—P. R., a Negro female, 4½ years old, was admitted to the Flower and Fifth Avenue Hospitals on Aug. 19, 1949, with a provisional clinical diagnosis of mediastinal and subcutaneous emphysema secondary to an attack of bronchial asthma.

The child was first seen in December, 1948, when examination showed eczema of the face, congenital cataract of right eye, and heart murmur which was interpreted as due to patent interventricular septal defect. Family history revealed that the mother had hay fever and suffered from asthmatic attacks. The baby was born prematurely, with a weight of 2,268 grams. Eczema of the face was first noted in early infancy and was controlled when milk was boiled, and when tomato, fruit juice, and chocolate were eliminated from diet. Beginning at 2½ years, the child exhibited monthly seizures of the petit mal type.

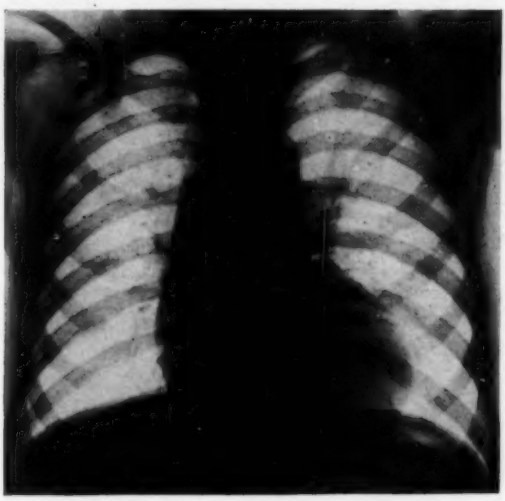

Fig. 4.—Extravasations of air in subcutaneous tissues of neck and thoracic wall (Case 3).

Two days prior to hospitalization, the child exhibited wheezing respirations and cough. The next day, respiratory embarrassment increased, with the development of fever. On the morning of referral to the hospital, it seemed to the mother that the child suddenly began to breath easier. Swelling of the neck and the presence here of crepitations were now noticed by the family physician.

On admission, temperature was 100° F. (37.7° C.) and pulse 108. Respirations were 44 and were somewhat labored and wheezy. The child was cyanotic, and comfortable only when her head was hyperextended. Crepitus was elicited in the subcutaneous tissues of the thoracic wall and of the neck, more so anteriorly. Lungs showed hyperresonance and distant breath sounds, with forced expiratory wheezes. Few scattered coarse moist râles were also heard. Heart sounds were faint. A harsh, systolic murmur was audible to left of the sternum, with maximum intensity in third and fourth intercostal spaces. Blood pressure was 100/70. Mucous membranes of nose and throat were moderately congested.

Roentgenograms of chest in the posteroanterior and lateral views showed both lung fields to be well aerated and clear. Collections of air were visible in the superior mediastinum and in the tissues of lateral chest wall and neck. There was no shifting of mediastinum.

Urine was negative. Hemogram showed 5,800,000 red blood cells and hemoglobin of 102 per cent. White cell count was 7,200, of which 55 per cent were polymorphonuclear neutrophiles, 4 per cent eosinophiles, and 41 per cent lymphocytes.

The child was placed in an oxygen tent and penicillin was administered. Therapy was also given to terminate asthmatic attack. Improvement was noted the following day.

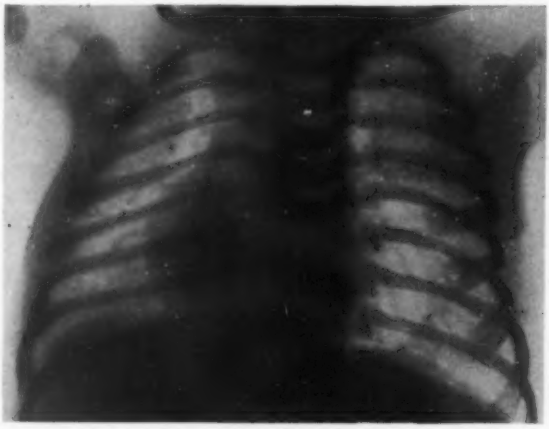

Fig. 5.—Posteroanterior view of chest showing mediastinal emphysema left pneumothorax, and shifting of cardiac silhouette to right (Case 4).

Fig. 6.—Lateral view showing collection of air in anterior mediastinum (Case 4).

Respirations were easier; expiratory wheeze persisted. Subcutaneous emphysema was evident only in neck tissues. Temperature remained below 100° F. (37.7° C.). On third hospital day, administration of oxygen was stopped. Roentgenograms of lungs, four days after admission, still showed subcutaneous collections of air, but no mediastinal emphysema (Fig.

4). The girl was discharged on Aug. 25, 1949. Most likely, the escape of air into the mediastinum and the subcutaneous tissues was brought about by the asthmatic bronchitis. Of interest is the mother's observation of the sudden abatement of the labored breathing just prior to the detection of extravasations of air into the subcutaneous tissues of neck and thoracic wall.

CASE 4.—A female infant, C. T., was delivered at full term with a birth weight of 3,000 grams at the Metropolitan Hospital on Aug. 18, 1949. The mother was a healthy primipara. Labor lasted twenty hours. Delivery was spontaneous from a left occiput position. Considerable amniotic fluid was aspirated. Cyanosis was present, and respirations were weak, shallow, and about 120 to 150 per minute. The chest wall appeared splinted in inspiration. Percussion note was hyperresonant. Few fine crepitant râles were heard on right side posteriorly. Roentgenograms of chest in posteroanterior and lateral positions showed extravasations of air in the anterior mediastinum. There was an absence of lung markings in the left lateral thoracic cage, indicative of a pneumothorax. Heart was shifted over into right side of chest (Figs. 5 and 6).

The infant was placed in an incubator. Continuous oxygen was given with improvement of color. Fluids were administered by hypodermoclysis. Feedings were withheld for first forty-eight hours. Penicillin was injected intramuscularly. On second postnatal day, color was good while the baby received oxygen. Respiratory rate was 80 to 90 per minute. Since there was no undue dyspnea, mediastinal aspiration was deferred. On third postnatal day, percussion note was hyperresonant. Tachypnea was present, but no cyanosis. Heart sounds were heard loudest on the right side. On the fifth postnatal day, dyspnea, tachypnea, and cyanosis had subsided. Oxygen therapy was no longer necessary. Roentgenogram of the chest showed a residual pneumothorax, but examination of the lungs elicited no abnormal physical signs. The infant was discharged home at two weeks of age in good condition, weighing 454 grams more than at birth.

The circumstances underlying development of mediastinal emphysema and pneumothorax in this baby were probably related to attempts at artificial resuscitation and removal of the aspirated amniotic fluid.

CASE 5.—M. H., a 16-month-old white female infant, who weighed 10.9 kilograms, was admitted to the hospital by Dr. Bret Ratner on March 2, 1950, for cough of 3 days' duration and dyspnea of 1 day. There was a past history of asthmatic attacks, the initial episode stated to have dated back to 6 weeks of age. Several attacks were severe enough to require hospitalization.

On admission, the girl's temperature was 37° C. (98.6° F.), with a later rise to 39.5° C. (103.4° F.). Cyanosis was prominent. Respirations varied between 50 and 60, and substernal retraction was evident. A mucoid nasal discharge, moderate congestion of the pharynx, and enlargement of the tonsils were present. Inspiratory and expiratory dry râles were heard in both sides of the chest. The left side of the chest appeared splinted. Breath sounds were diminished in the area of the left upper lobe. Shifting of the heart was not apparent.

Blood count showed 4,000,000 red cells and hemoglobin of 75 per cent. White cells were 21,800, with 81 per cent neutrophiles, 13 per cent lymphocytes, and 6 per cent mononuclear cells. Sedimentation rate was 24 mm. in one hour. Urine reacted positively to albumin and acetone tests, and contained finely granular casts. Roentgenograms of the chest revealed clouding of the upper-left pulmonary field. In addition, mediastinal emphysema and a pneumopericardium were seen (Fig. 7).

The child was placed in an oxygen tent and given chloramphenicol (Chloromycetin) orally and penicillin intramuscularly, with relief of symptoms. The temperature declined to normal in forty-eight hours. On the second day of hospitalization, air was palpated in the soft tissues of the neck. This subcutaneous emphysema was visualized in subsequent roentgenograms of the chest, which also showed resorption of the escaped air from the mediastinum and pericardium, and clearing of the pneumonic process in the left-upper lobe.

This case illustrates again the relationship of acute asthmatic attacks and infection to the development of sudden pulmonary interstitial and mediastinal emphysema.

Fig. 7.—Posteroanterior view of chest showing pneumopericardium.

## COMMENT

Pulmonary interstitial and mediastinal emphysema, or airblock, is defined by the Macklins[3, 4] as interference with normal functions of respiration and circulation by extraneous collections of air in the interstitial tissues of the lungs, the mediastinum, and their fascial extensions. Most instances of airblock are benign, with spontaneous recovery. Under certain circumstances, directly related to the degree of respiratory and circulatory embarrassment induced by pressure of the escaped air, the condition may become malignant with consequent fatality.

According to the Macklins,[3, 4] and Fisher and Macklin,[6] two main forces contribute to airblock. The first concerns interference with circulation, particularly the pulmonary circulation. Air bubbles of varying sizes induce compression of the intrapulmonary arteries and veins, the heart and great vessels of the mediastinum. The second concerns interference with respiratory movements of the lung from the locking or splinting action of air in the interstitial tissues of the lungs. Inflation or deflation are inhibited and airlock occurs. Hyperinflation, or overdistention of the alveoli bordering upon blood vessels may build up an intra-alveolar pressure greater than that within the blood vessels. The pressure gradient created may result in rupture of the alveolar bases, with escape of air into perivascular sheaths. A similar gradient and compression effect may also occur during a lowering of pressure in the pulmonary circulation. The air may then dissect along artificial channels to the hilar regions, with the production of mediastinal emphysema. Furthermore, if the

pressure becomes sufficiently great, the air may be forced out into the subcutaneous tissues or into one or both pleural cavities, with establishment of pneumothorax.

Hamman[1, 2] states that one-third of the cases of pulmonary interstitial and mediastinal emphysema are complicated by pneumothorax. Congenital weakness of the alveolar wall may predispose to rupture of air into the perivascular sheaths and explain recurrence of the condition in some individuals. Miller[7] states that most cases of spontaneous pneumothorax show no evidence of underlying pulmonary pathology. The Macklins[3, 4] are of the opinion, however, that in most instances of idiopathic pneumothorax the underlying causes are not found because of incomplete investigation. Then, too, time may elapse between the onset of the interstitial emphysema and the pneumothorax, so that the precipitating cause appears unrelated to the presenting symptoms. Among the precipitating factors leading to airblock and to pneumothorax should be listed overinflation of the lungs, artificial resuscitation, insufflation anesthesia, atelectasis, violent strain, and blocked airway. Predisposing factors may be present, such as acute or chronic respiratory infection, asthma, and cough.

*Occurrence.*—Except for the cases of pulmonary interstitial and mediastinal emphysema in newborn infants and those following tracheotomy, the mechanism of which has been described by Forbes, Salmon, and Herweg,[8] airblock in infants and children is considered infrequent. According to the reports of Fagin and Schwab,[9] Taschman,[10] Matthews,[11] and Babington,[12] it is characteristically a condition of later life, and is seen chiefly in males from 15 to 40 years of age. Yet it occurs often enough in infants and young children to warrant a knowledge of the condition by the clinician.

Iglauer[13] reported a case in a 3-year-old girl with a history of a slight cold and cough for a few hours previous to the onset of symptoms. Motsay and Dowdell[14] reported a case in a 5-month-old infant with measles complicated by a persistent dry cough. Other reports are those by Taschman[10] in a 6-week-old infant with a lung abscess, by Higgins[15] in a 3-week-old baby with a ruptured perinephritic abscess, by Scott[16] in a 2-year-old child following kerosene ingestion, and by Heber[17] in a 5-month-old infant with a pneumatocele complicating pneumonia.

*Clinical Picture.*—In adults, the symptoms of pulmonary interstitial and mediastinal emphysema appear suddenly, with mild to severe precordial pain which radiates outward, a feeling of tightness in the chest, and shortness of breath upon exertion. Dyspnea, cyanosis, and falling blood pressure may serve to confuse the condition with that of acute coronary heart disease. The sign of Hamman[2] may occur, in which the patient is aware of peculiar crackling, bubbling, or crunching sounds in the chest. Griffin[18] considers Hamman's sign diagnostic of mediastinal emphysema. It may be heard without a stethoscope, and is probably due to sounds made by bubbles of air in the interstitial tissues overlying the pericardium, with synchronization of these sounds with the heartbeat. Monroe and Webb[19] have emphasized that dyspnea and cyanosis are usually not seen in the adult. Examination reveals the usual physical findings

of pneumothorax. Subcutaneous emphysema of the chest wall may be present. There is an absence of general reaction, such as fever, leucocytosis, and increased sedimentation rate. The respiratory and pulse rates may be increased. Diagnosis is confirmed by roentgenography.

The clinical picture in infants differs greatly from that in adults. The outstanding symptoms are dyspnea and cyanosis. Fever may also be present. Expiratory excursions are limited, with an increase in the respiratory rate. The heart sounds may be distant. Salmon[20] points out that Hamman's sign is heard less frequently in infants. Of thirty-one infants with cases that complicated tracheotomy, Forbes, Salmon, and Herweg[8] found only six with Hamman's sign. Signs of complicating pneumothorax may be elicited. If bilateral pneumothorax is present, a shift of the mediastinum may not take place. In severe cases, dyspnea and cyanosis may be so great that death ensues unless the increased pressure within the mediastinum is relieved. Fisher and Macklin,[6] and Salmon and Forbes[21] are of the opinion that the dyspnea and cyanosis are caused by the pressure of air on the great vessels, and more especially the veins. Whether or not pain is present is hard to determine in the infant.

Roentgenography of the chest in the posteroanterior view in instances of mediastinal emphysema may show the heart outlined by air. The mediastinal air may often be best visualized in the lateral view, although according to Salmon, Forbes, and Davenport,[22] this view may be misleading if pneumothorax is present under tension or if there is a herniation of the anterior mediastinum.

*Treatment.*—Treatment of the condition depends upon the severity of the symptoms. If few symptoms are present, no treatment may be necessary. Oxygen is indicated for relief of dyspnea and cyanosis. Aspiration of the mediastinum may be attempted if cyanosis and dyspnea are severe. Salmon and Forbes[21] state that this procedure should be reserved only for those cases that do not improve with simple measures. The observations of Forbes, Salmon, and Herweg[8] show that air may be present in the form of loculated bubbles of various sizes. Cautious exploration is therefore necessary to remove any quantity of air. Spontaneous rupture of the air in the mediastinum into the pleural space may give relief of symptoms. The resultant pneumothorax may serve to stop further collection of air in the mediastinum by causing collapse and compression of the area of alveolar rupture. Chemotherapy or antibiotics are indicated in prevention of infection of the mediastinum or along the course of the blood vessels, especially if a pulmonary infection is present.

## CONCLUSIONS

In the differential diagnosis of unexplained acute respiratory and circulatory embarrassment in infancy with dyspnea and cyanosis as the predominant signs, the occurrence of pulmonary interstitial and mediastinal emphysema and of spontaneous pneumothorax should be borne in mind. History and physical signs do not always reveal the underlying condition. The cyanosis and dyspnea may at first be erroneously ascribed to disease of the respiratory tract, or to

disorder of the heart. Collateral roentgenographic studies will, however, prove of value in the early detection of extraneous collections of air in the mediastinal areas and in the pleural spaces.

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# CONGENITAL AURAL FISTULA

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CONGENITAL fistula of the external ear is a comparatively common but easily overlooked developmental anomaly. The condition is variously described as fistula auris congenita, congenital auricular sinuses, and congenital auricular fossa. Although many reports have cited the occurrence of this condition, it is not recognized by many physicians. Comparatively few reports have appeared in the pediatric literature.[1, 2]

The defect consists essentially of an opening at the anterior margin of the helix or some juxtaposition and a rather short sinus tract directed internally. Since the first description of the anomaly by Heusinger in 1864, many reports have appeared in the German,[3] British,[4, 5] and American[6, 7, 8] literature. Comprehensive papers on the subject have been reported by Congdon[9] and his associates, and Selkirk.[1] We desire to report several cases in Negro children and to emphasize its hereditary tendency and possibility of important clinical complications.

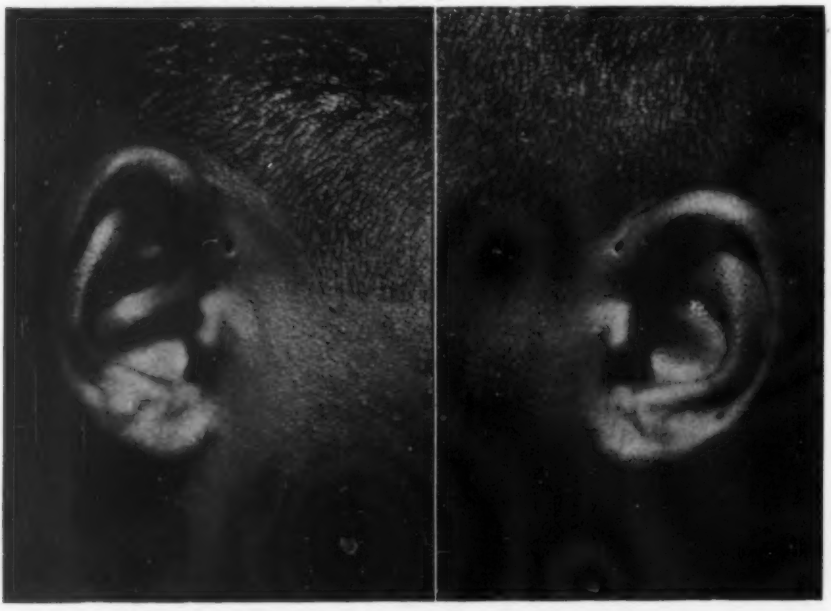
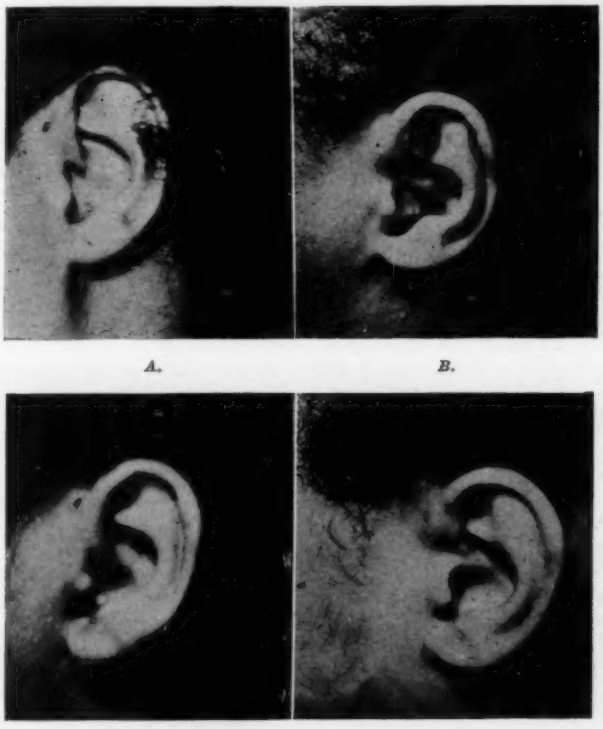


Fig. 1.—Fistulas at the anterior margin of the helix in two brothers. Sinus tracts measuring a few millimeters were present. However, there were no complication except for the discharge of a small amount of thin white secretion upon digital pressure near the orifices.

From the Department of Pediatrics, Howard University School of Medicine and the Pediatric Service of Freedmen's Hospital.

*A.* *B.*

Fig. 2.—A bilateral marginal helicine fistula in a child (*A*) and a similar condition (unilateral) in his mother (*B*).



*A.* *B.*

*C.* *D.*

Fig. 3.—A marginal helicine fistula in a mother (*A*) and in her three siblings. The photographs of two of the siblings (*B*, *D*) show a swelling of the tissue surrounding the fistulas. These swellings were intermittent. A thin, whitish secretion could be expressed on pressure but there was no evidence of suppuration.

Fig. 4.—A fistula of the common type in a 2-month-old mongolian idiot.

Fig. 5.—This is a marginal helicine fistula complicated by suppuration in a 10-year-old girl. The sinus opening is partially obscured by the swelling. The abscess was treated surgically.

Fig. 6.—A preauricular appendage in an infant. This anomaly was hereditary and was reported in several ancestors.

## DISCUSSION

Several theories have been proposed to explain the origin of congenital auricular fistula. The initial concept was that it resulted from a developmental imperfect closure of the first branchial cleft. Embryological studies have tended to disprove this theory.[9] The current opinion is that these openings are the result of the failure of complete fusion of the six primary tubercles which in early embryonal life are destined to become the external ear. These six rudimentary tubercles unite to form the tragus, crus of the helix, anti-helix, antitragus, and lobule, respectively. (Fig. 7.)

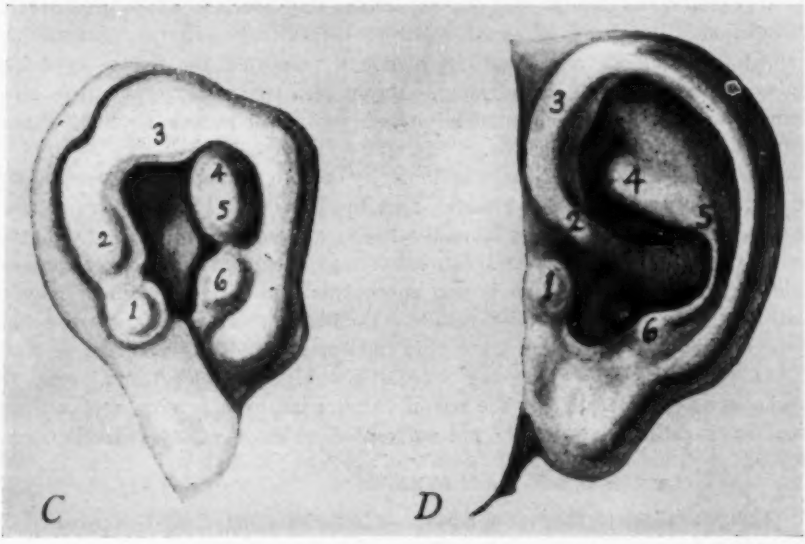



Fig. 7.—Development of the human auricle (partly after His), from Arey, *Developmental Anatomy*, ed. 4. *C* at 15 mm.; *D*, adult. Numbers 1 to 6 represent elevations on the mandibular and hyoid arches which respectively become: 1, tragus; 2, 3, helix; 4, 5, antihelix; 6, antitragus. (Reproduced by permission of W. B. Saunders Company.)

Clinically the fistulas may be classified according to the location as anterior marginal helicine, crural, posterior helicine, lobular, preauricular, and postauricular. The most common type is that found at the anterior margin of the ascending limb of the helix. This type is most prone to become infected (Fig. 5). They may be bilateral or unilateral. The external openings may be oval, round, or mere slits. In fistulas examined with a probe, the direction of the tract was found to be predominantly downward, slightly inward, and often directed a little forward or backward. Most depths reached up to 7 mm. Congdon[9] and his associates reported a few fistulas of 9 mm. in depth, but they pointed out that if the canal bends, a stiff probe may not reach the end of the tract.

The reported incidence is variable. Urbantschitsch[10] reported twelve cases among 2,000 persons. Congdon, in his study of Oriental races, found a 4 per cent incidence in some racial stocks and a 6 per cent in others. Sel-

kirk's group of 172 patients showed an incidence of 0.9 per cent in 3,660 white children and an incidence of 5.2 per cent in 346 Negro children examined. The ratio of male to female children was approximately 1:4 for both races. This condition has a distinct hereditary nature as is illustrated by the cases reported here.

Other congenital defects which have been noted in association with congenital auricular fistula include preauricular scars and auricular appendages in the form of tubercles or cartilaginous nodules (Fig. 6). These projecting tubercles are thought by the writers and others to be related embryologically to congenital aural fistulas. In our experience they are most often preauricular in location. We have observed a strong hereditary pattern. Ruttin[3] described a family in which certain members presented the fistula type and others the tubercle type of anomaly. Major developmental disturbances other than those of the ear and branchial system are rarely encountered in subjects bearing congenital aural fistula.

Histologically, on section, the majority of the sinuses consist essentially of skin, hair, and sebaceous glands. Due to obstruction of the openings from desquamating epithelial cells from the lining and mucoid secretions from the ducts, suppuration and abscess formation may occur. In the event that the true nature of the condition is not appreciated, palliative treatment may be instituted with uniformly poor results. Definitive treatment entails the complete excision of the sinus tract. In noncomplicated cases where cosmetic effects are desired or where the mucoid discharge becomes troublesome, the tracts may be obliterated by the use of fulguration or sclerosing agents. Surgical intervention is generally not warranted unless symptoms develop.

## SUMMARY

Congenital aural fistula represents a frequently overlooked hereditary defect which becomes of clinical importance when local infection occurs. In cases of swelling or abscesses of or near the ear, physicians would do well to investigate the possible presence of congenital auricular sinuses and fistulas in order to insure proper and successful treatment.

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# Case Reports

## FEMALE PSEUDOHERMAPHRODITISM DUE TO CONGENITAL ADRENAL CORTICAL HYPERPLASIA WITH ASSOCIATED ADDISONIAN-LIKE SYMPTOMS

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SINCE 1939, when the condition was first recognized, there have been reported sporadic cases of female pseudohermaphroditism, or male precocious development due to embryonic hyperplasia of the adrenal glands associated with Addisonian-like symptoms due to corticoadrenal insufficiency.[1-10] From the cases reported it would appear that the condition is predominant in the male, the reason for this being unknown.

We feel that additional case reports of this clinical entity are necessary to further arouse the physician's awareness of its existence. We, therefore, present the following case.

### CASE REPORT

This is the case of D. E., a white female infant, whose first admission to Akron Children's Hospital was on July 29, 1949, at the age of 7 weeks. The infant had been seen in the admitting room that same day because "the child hasn't been able to keep anything in her stomach." The mother stated that the infant had presented a feeding problem since birth, vomiting after meals, and bouts of colic. The day of admission the infant had had two episodes of turning pale; one had occurred after vomiting and one after screaming. These were the immediate cause for bringing the infant to the hospital.

*Relevant History.*—The mother was a 27-year old woman who was gravida ii, para ii. The nine-month pregnancy had been an uncomplicated one; labor was eight hours long. The delivery was a normal one under ether anesthesia, with spontaneous respiration of the newborn infant. Low forceps were used, the infant being born in a vertex presentation. The birth weight of the infant was 8 pounds, 9 ounces. While in the hospital, the infant was formula-fed, ate well, but lost weight. At 11 days of age, the patient was discharged weighing 7 pounds, 13 ounces. At home the infant was placed on Baker's Milk formula, 4 ounces every four hours. In reiteration, the infant presented a feeding problem, and at 6 weeks of age had been dehydrated and still weighed 7 pounds, 13 ounces. The formula was changed after two to three weeks from Baker's Milk to evaporated milk 13 ounces, boiled water 20 ounces, because the infant's face had broken out in a rash.

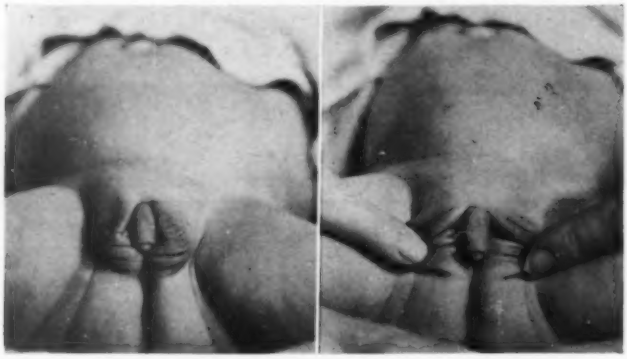
*Admission Physical Examination.*—Physical examination on admission revealed a pale infant with dusky, cold skin. The remainder of the examination was negative except for a very enlarged clitoris. Dehydration was not noted.

*Laboratory Data.*—On July 29, 1949, these were the laboratory results: red blood count 4,100,000; hemoglobin 11.5 Gm. or 71 per cent; color index 0.8; white blood count 7,300 with 49 per cent polymorphonuclears, 45 per cent

Read in part at the Staff Meeting, Akron Children's Hospital, Sept. 14, 1949.
From Children's Hospital, Akron, Ohio.

lymphocytes; tuberculin 1 to 1000-negative; Kahn and Kline tests were negative; nasopharyngeal culture showed *Staphylococcus aureus*; chest x-ray revealed thymic enlargement with posterior displacement of the trachea; pneumonic infiltration was seen in the right lower lobe; skull x-ray revealed an essentially normal skull.

On July 30, 1949, urinalysis and microscopic examination results were normal.



*A.* *B.*

Fig. 1.—*A*, The enlarged clitoris and labia majora give the outward appearance of male genital organs. *B*, The labia major have been separated, showing the true picture of the region.

Fig. 2.—Genitogram demonstrating the communication between the vagina and urethra. The bladder and vagina were filled simultaneously by injection of diodrast through the catheter. (Right oblique.)

*Treatment.*—The infant was placed on the same evaporated milk formula as previously stated, and vitamins. Oxygen and penicillin 5,000 units every three hours were started because the episodes of turning pale suggested a possible aspiration pneumonia. Clyses of 2.5 per cent glucose in Hartman's solution, 100 c.c. every eight hours were given and an intravenous injection of 125 c.c. of 5 per cent glucose in Hartman's solution was given on July 29, 1949. Another intravenous injection of 150 c.c. of 5 per cent glucose in Amigen was given on Aug. 1, 1949.

*Course in the Hospital.*—Temperature ranged from 98.6° to 101.4° F. Weight on admission was 7 pounds, 14¼ ounces; and at the time of discharge, 8 pounds, 1 ounce. At no time was there vomiting during the hospital stay,

and the appetite gradually increased so that while the infant took only 11 ounces the first twenty-four hours she was hospitalized, she was taking from 30 to 33 ounces per twenty-four hours at the time of discharge. In spite of oral intake, clyses, and intravenous injections, the infant was still pale and dehydrated at the time of discharge on Aug. 5, 1949. The discharge diagnosis was "feeding problem."

On Aug. 16, 1949, this infant was readmitted because of failure to gain weight, and dehydration. Her weight was now 8 pounds, 5 ounces, though the previous week she had weighed 8 pounds, 10 ounces. Since her last admission, the infant had vomited every three to four days. Her bowel movements had been normal.

*Physical Examination on Admission.*—Examination on admission showed a thin, undernourished, chronically ill-appearing, dehydrated infant who did not follow light or motion. The fundi were normal. Inspection of the external genitals again revealed a markedly enlarged clitoris (Fig. 1, *A* and *B*) and the site of the urethral meatus was not located. The other systems were found to be normal except for a sunken anterior fontanel and muscle hypotonia.

Because of the failure to gain weight, the tendency to dehydration, the gastrointestinal disturbances, the grayish appearance of the patient, the failure to respond to changes in formula and fluids, and the markedly enlarged clitoris, the possibility suggested itself that this might be a case of pseudohermaphroditism due to congenital adrenal cortex hyperplasia of the androgenic zone with associated secondary cortical insufficiency. Laboratory and x-ray studies revealed findings confirming the provisional diagnosis (Table I and Fig. 2).

TABLE I. LABORATORY AND X-RAY DATA USED IN ESTABLISHING THE DIAGNOSIS

| |
|---|
| *Laboratory Findings:* |
| 1. $CO_2$ combining power: 10 meq. per liter |
| 13 meq. per liter |
| 2. Nonprotein nitrogen: 87 mg. per cent |
| 3. Serum sodium: 125 meq. per liter |
| 4. Plasma chlorides: 86 meq. per liter |
| 5. Whole blood chlorides: 73 meq. per liter |
| 6. Ketosteroids: 8 mg. per 24-hour urine specimen |
| 7.3 mg. per 24-hour urine specimen |
| 7. Fasting blood sugar: 90 mg. per cent |
| 8. Glucose tolerance test: normal |
| 9. Spinal fluid: normal |
| *X-ray Studies:* |
| 1. A genitogram and cystogram showed a normal appearance of the bladder and a congenital deformity with communication between the vagina and urethra. |
| 2. An intravenous pyelogram failed to show evidence of a functioning kidney on either side. However, retrograde pyelography showed a normal appearance of the collecting systems of both kidneys. No difficulty in passing the urethral catheters was found. This, along with normal urinary constituents, eliminated the possibility of a congenital renal defect. |

Meanwhile, the patient was taking an evaporated milk formula poorly, regurgitating, and remaining very dehydrated in spite of regular infusions of 2½ per cent glucose in distilled water and 2½ per cent glucose in lactate Ringer's solution in adequate amounts.

On Aug. 18, 1949, in accordance with our diagnosis, the patient was placed on desoxycorticosterone acetate 2.5 mg. intramuscularly daily, and 3 Gm. table salt were added to the formula.

By Aug. 20, 1949, a marked improvement was apparent in the appearance of the infant. She was no longer listless; she cried vigorously, was kicking, and was moving her hands through the air. The skin color was now pinkish, the

anterior fontanel was not depressed, the eyes were losing their sunken appearance, and the dark rings under the eyes were beginning to disappear.

By Aug. 21, 1949, the clyses were cut, the infant was alert, eyes were bright, and the infant was holding down all 30 ounces of the evaporated milk formula daily. In addition, Pablum and applesauce had been added to the diet and these were taken hungrily. On August 22, because the weight gain was slow and the patient would at times turn pale and listless again, the desoxycorticosterone acetate was increased to 2.5 mg. twice daily. Laboratory studies repeated on Aug. 26, 1949, one week after therapy was begun (Table II), showed

TABLE II. LABORATORY DATA AFTER ONE WEEK ON DESOXYCORTICOSTERONE ACETATE

| | |
|---|---|
| 1. Serum sodium: | 123 meq. per liter |
| 2. $CO_2$ combining power: | 10 meq. per liter |
| | 14 meq. per liter |
| 3. Glucose tolerance test: | normal |
| 4. Nonprotein nitrogen: | 40 mg. per cent |
| 5. Fasting blood sugar: | 100 mg. per cent |
| 6. Plasma chlorides: | 91 meq. per liter |
| 7. Uric acid: | 6 mg. per cent |
| 8. Serum cholesterol: | 104 mg. per cent |
| Cholesterol esters: | 69 mg. per cent |

little change in the findings, even though clinically the patient's condition was greatly improved as compared to her original appearance, and the weight was now 8 pounds, 13 ounces. It was then discovered on August 29, that the patient, through error, had received no added salt in her formula from August 23 through August 29. This was rectified; 4 Gm. of salt were added to the formula, and, because it was felt that a better clinical response was possible, the desoxycorticosterone acetate was increased to 5 mg. once daily and 2.5 mg. once daily on Aug. 30, 1949. Then the patient's weight rapidly increased from 8 pounds, 14 ounces to 11 pounds, 10¼ ounces on Sept. 27, 1949. There was no evidence of edema or cardiac enlargement. The patient held her head up, followed light and a moving finger, smiled occasionally, was alert, had good color, did not vomit, was not dehydrated, had normal stools, and had good muscle tone (Fig. 3, *A*).

TABLE III. LABORATORY FINDINGS SIX WEEKS AFTER THE INSTITUTION OF HORMONAL AND SALT THERAPY (AUG. 18, 1949 TO SEPT. 27, 1949)

| | |
|---|---|
| 1. $CO_2$ combining power: | 16 meq. per liter |
| | 17 meq. per liter |
| 2. Nonprotein nitrogen: | 30 mg. per cent |
| 3. Serum sodium: | 134 meq. per liter |
| 4. Whole blood chlorides: | 76 meq. per liter |
| | 83 meq. per liter |
| 5. Fasting blood sugar: | 100 mg. per cent |
| 6. Glucose tolerance test: | normal |
| 7. Electrocardiogram: | no evidence of potassium intoxication; congenital heart lesion (?) |

At this time the laboratory work was repeated. The marked improvement in laboratory findings after six weeks of therapy when compared to those before the institution of therapy is easily seen when Tables III and I are compared. An electrocardiogram was taken for evidence of potassium intoxication effect on the heart since potassium determinations as such in our laboratory were not reliable.

Supportive therapy had included four blood transfusions, streptomycin for an *Escherichia coli* urinary infection which cleared after one week of therapy, urine culture on Sept. 2, 1949, showing no growth, and penicillin for

a right-sided bronchopneumonia developing on September 21, which cleared gradually.

Following the completion of laboratory studies the desoxycorticosterone acetate and added salt in the formula were discontinued. Within two days after discontinuing the therapy the infant appeared paler, the eyes were a bit sunken, and there had been a weight loss of 6 ounces. Thereafter the weight fluctuated between 11 pounds, 14 ounces, and 10 pounds, 8 ounces for the next three weeks until medication was reinstated. The infant gradually became

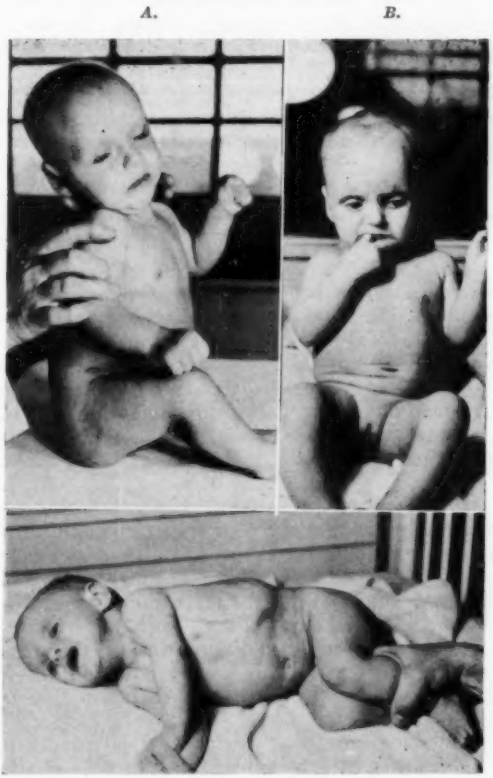



Fig. 3.—*A*, Taken the day therapy was stopped, showing the healthy appearance of the infant. *B* and *C*, Taken three weeks after therapy was discontinued, showing the marked relapse in the infant's condition. Note the sunken fontanel, the sunken eyes, the pinched expression, and the loose, dry skin over the abdomen.

listless and irritable, her anterior fontanel became sunken, her lips were dry and pinched, her skin loose and dry. Respirations became rapid and deep. The infant's intake decreased to about 15 to 18 ounces of formula daily with a poor intake of solids, but there was no vomiting or diarrhea. Associated with these findings were a falling red blood count and hemoglobin, from 4,680,000 red blood count and 90 per cent hemoglobin on September 24; to 3,980,000 red blood count and 71 per cent hemoglobin on October 8. The extent of the change in

the appearance of the infant can easily be seen by comparing Fig. 3,*A* taken the day therapy was stopped, with Fig. 3,*B* and *C*, taken three weeks after therapy was discontinued.

Laboratory data were repeated twice during the three-week period of therapy at ten-day intervals. The results are summarized in Table IV showing a fall in serum sodium and plasma chlorides, a high normal nonprotein nitrogen, and an increasing carbon dioxide-combining power which cannot be explained since clinically the patient was having an acidotic type of breathing.

The infant was restarted on desoxycorticosterone acetate and added salt to the diet on Oct. 18, 1949, and to date has made satisfactory progress.

TABLE IV. LABORATORY DATA TEN DAYS (*A*) AND 20 DAYS (*B*) AFTER THE DISCONTINUATION OF HORMONAL AND SALT THERAPY

| | GLUCOSE TOLERANCE TEST | $CO_2$ COMBINING POWER (MEQ. PER LITER) | FASTING BLOOD SUGAR (MG. PER CENT) | NONPROTEIN NITROGEN (MG. PER CENT) | SERUM SODIUM (MEQ. PER LITER) | PLASMA CHLORIDES (MEQ. PER LITER) |
|---|---|---|---|---|---|---|
| A. | Normal | 15 | 90 | 33 | 125 | 85 |
| B. | Normal | 19 | 100 | 40 | 116 | 79 |

## DISCUSSION

Excessive adrenal androgen hormone is secreted if the adrenal glands undergo hyperplasia during fetal life. In females, this adrenal dysfunction has virilizing effects which are manifested at birth by rather typical pseudohermaphroditic changes.

Internally these infants possess ovaries, a vagina, a uterus, and Fallopian tubes. However, instead of having a separate vagina and urethra as in ordinary females, the genital duct opens up into the urethra as in the male so that there is a communication between the vagina and urethra—a urogenital sinus. (Fig. 2.)

Externally, at first glance, one usually feels he is looking at a hypospadias. This is because the clitoris is markedly enlarged, resembling a true penis, and the labia majora, which are heavily grooved, fall together beneath the clitoris, simulating a scrotum. (Fig. 1, *A* and *B*.) On separating the labia majora and elevating the clitoris a shallow vulvar depression is seen between the labia minora into which the urogenital sinus opens (Fig. 4).

In addition to this abnormal sex differentiation, the urinary excretion of 17-ketosteroids, representative of androgen production, is greatly increased from birth. Later years mean progressive virilization due to the continuous excessive androgen secretion.

In the male, the same hormonal dysfunction is usually not recognized at birth because of the absence of external manifestations. However, rapidly progressive penile enlargement is noticed from 3 months to 3 years of age, and thereafter precocious isosexual development occurs during adolescence. Characteristically, the testes are usually immature because excessive adrenal androgen excretion inhibits testicular development.

In occasional cases, as in our patient, the congenitally increased androgenic activity of the adrenals is accompanied by symptoms and electrolyte changes of adrenal cortical insufficiency. At first this was attributed to a suppression by the adrenal androgen—producing cells of the other cells having carbohydrate-controlling and salt regulation (through sodium and potassium tubular reabsorption) properties. Recent investigations, however, suggest that the electrolyte changes and Addisonian-like symptoms are due to the secretion by the adrenal of a hormone causing excessive salt *excretion*.

In either case, whether by decreased retention or by increased excretion, sodium and chloride are lost in abnormal quantities, giving a low blood concentration of these electrolytes. Conversely, the potassium plasma level rises. Unfortunately, reliable potassium determinations were not available in our laboratory. Due to these electrolyte changes, extracellular fluid volume decreases, resulting in dehydration, hemoconcentration, and low blood pressure, among other changes. Renal function becomes impaired because of the circulatory failure, so that retention of other blood constituents such as nonprotein nitrogen occurs. Acidosis prevails because of the sodium loss and the kidney's decreased ability to rid the body of acid metabolites.

Interestingly enough, repeated fasting blood sugars and glucose tolerance tests were normal in our case. Yet a urinary uric acid excretion determination done on Aug. 26, 1949 (Table II) showed a much higher than normal uric acid output indicative of increased tissue protein catabolism. It is known that the adrenal carbohydrate regulating hormone, when in excess, results in a tendency toward hyperglycemia and also accelerated nitrogen catabolism. We, therefore, could not explain the high uric-acid level in the absence of hyperglycemia. Unfortunately, only one urinary uric-acid determination was done.

The adrenal cortical hormones are said to be derived from cholesterol. Can the low cholesterol value (Table II) be explained by its excessive use to form the increased quantity of androgen hormone?

Fig. 4.—The labia majora are separated and the clitoris is elevated showing the vulvar depression between the labia minora. Note the similarity to a hypospadial penis. The urogenital sinus opening is hidden behind the posterior commissure.

Clinically, the picture of the associated adrenal cortical insufficiency may include marked dehydration and failure to gain weight or weight loss despite adequate intake and repeated attempts at changing the feeding formula; gastrointestinal disturbances such as anorexia, vomiting, abdominal cramps, and diarrhea; circulatory collapse and anuria; pigmentation of the skin and mucous membranes as in true Addison's disease, restlessness, and temperature elevations. Hypoglycemia due to decreased production of carbohydrate-regulating hormone has not been reported.

The treatment of this clinical entity has included desoxycorticosterone acetate (the electrolyte-balancing hormone of the adrenal) which increases sodium retention and decreases potassium retention; adrenal cortex extract; added salt to the diet; sodium bicarbonate or sodium lactate to combat the low bicarbonate concentration. These may be given alone or in combination, depending on the individual case. The dosages of each must also be adjusted by trial and error for each patient. In the milder cases patients can be carried on just a moderate salt intake, whereas, in more severe cases the patients require the use of hormonal therapy in addition.

Treatment of the pseudohermaphroditism is practically nil. The excessive androgen production cannot be curbed medically at the present time, or surgically even by subtotal adrenalectomies. In our case, we have discussed the matter with the parents, and it has been decided to allow nature to take its course. Consequently, since progressive virilization will occur, the patient will be raised as a male. Possibly in the future, plastic operations to correct the outward appearance of the genital organs will be done.

## SUMMARY

1. A case of female pseudohermaphroditism due to congenital adrenal hyperplasia with associated symptoms of cortical insufficiency is reported.
2. The clinical and laboratory aspects of this entity are discussed.
3. Recommendations for therapy are presented.

We are gratefully indebted to Miss Pauline Williams, laboratory technician at Akron Children's Hospital, for the laboratory determinations, to the Gynecology Laboratory, University of Michigan Hospitals, for the 17-ketosteroid determinations, and to Dr. Paul Weygandt, of our house staff, for the photographs.

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# MOLLUSCUM CONTAGIOSUM TREATED WITH AUREOMYCIN

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AN 11-year-old boy, J. B., in the summer of 1949 developed a few wartlike growths in the region of his right shoulder. Their number increased steadily until Dec. 12, 1949, when he was first seen by me. No treatment of any kind had been given up to this date.

The skin lesions presented all characteristics of molluscum contagiosum and numbered about eighty; three of them showed signs of secondary infection probably as a result of scratching.

In order to spare the boy the discomfort of curetting so many molluscа, a therapeutic trial with aureomycin was suggested to which the patient's mother consented. On Dec. 17 and 18, 1949, the boy received 250 mg. of aureomycin every six hours, a total of 2.0 Gm. No local treatment was prescribed. When seen on Dec. 23, 1949, the majority of the lesions had become flat and were about to disappear. However, six lesions had retained the appearance of smooth rounded nodules with a central depression, and seemed unaffected by the treatment. This state remained unchanged for the following three weeks during which no new lesions appeared.

On Jan. 13, 1950, a second course of treatment with aureomycin was given for two days using the same dosage as previously. Two days later, a distinct improvement was noted by the patient's mother. When last seen on Jan. 25, 1950, no typical molluscum could be found; all previous lesions appeared flat and dry.

## COMMENT

Molluscum contagiosum is caused by a filtrable virus.[1] Since other skin diseases of virus etiology such as herpes zoster seem to respond to aureomycin,[2] a therapeutic trial of this antibiotic in molluscum contagiosum was justified. This case responded promptly, if not to the first, to the second course of treatment. Perhaps a more prolonged treatment with smaller daily doses will yield better results. This single observation does not prove the efficacy of aureomycin in molluscum contagiosum, particularly since some cases heal spontaneously. Further investigation is required.

After completion of this observation, a recent report of another case treated by Guy, Jacob and Guy[3] with equally good results was brought to my attention.

## SUMMARY

One case of molluscum contagiosum healed promptly after treatment with aureomycin.

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# EXTRANASAL TYPE OF NASAL GLIOMA

## Report of a Case

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RARE congenital tumors occurring about the bridge of the nose and consisting of glial tissue have been described in the literature since about 1900.[1] These tumors have also been found inside the nasal cavities, and have presented themselves as nasal polyps which contained glial tissue. Some of them have been much larger tumors and, depending on their location, have been divided into intranasal gliomas[2, 3, 4, 5] and extranasal gliomas.[1, 2, 5, 6] Although the tumor probably does not represent an autonomous new growth, but rather an extracranial separation of nervous tissue early in uterine life, it has been called a nasal glioma and, for want of a better term, this one has been retained.[2, 3, 5, 6, 7]

Grossly the extranasal type presents itself as a rounded or dome-shaped, reddish, moderately firm, movable tumor which has been mistaken clinically for a hemangioma.[6]

Histologically the tumors consist of masses of delicate glial fibers which are found in the subcutaneous tissue and in the extranasal type extend up into the papillary layer of the corium.

Clinically the tumors are benign and are removed for cosmetic reasons. If the diagnosis is suspected before operation, x-ray pictures of the skull should probably be taken to demonstrate whether or not a defect of the skull exists in the region of the tumor, since encephaloceles occur in the same area with meningeal spaces which are continuous with the cranial cavity, and care should be taken to prevent a meningitis should the lesion prove to be an encephalocele.[6] True nasal gliomas should have no defect in the skull nor any connection into the cranial cavity.

### CASE REPORT*

The patient was a one-month-old white female infant who was brought to the hospital by the mother with the complaint of a growth on the infant's face which had been present since birth. The tumorous mass had not grown rapidly. The patient was a full-term infant who had weighed 7 pounds, 10 ounces at birth and had a normal delivery. Development since birth had been normal. She was the fourth child of the 22-year-old mother. The father was 25 years of age. The physical examination on admission showed a movable, reddish, moderately firm, rounded tumor which measured about 2 cm. across. The tumor involved the right side of the bridge of the nose and extended to the inner canthus of the right eye. The covering skin was not ulcerated. The impression of the pediatrician was that the tumor was a hemangioma. The remainder of the physical examination was essentially negative. (See Fig. 1.)

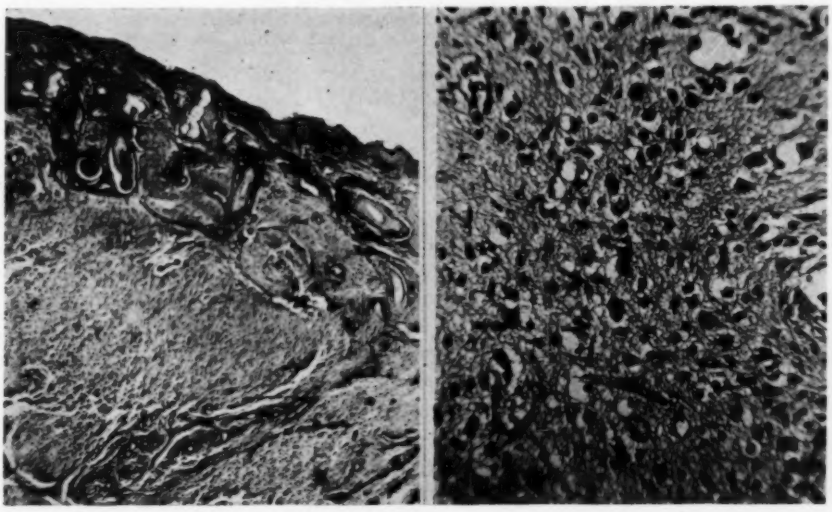
The patient was operated upon under general anesthesia and a transverse incision overlying the tumor mass was made, through which the tumor was enucleated. The mass appeared soft and friable and did not appear to be excessively vascular. The tumor was not attached to the periosteum of the nasal bones and did not appear to be locally invasive. The wound was closed with steel wire.

From the Department of Pathology, University of Texas Medical Branch, Galveston.

*Permission to use this case report was given by Dr. Truman G. Blocker, Jr., Professor of Plastic and Maxillo-facial Surgery, University of Texas.

Grossly the pathologic specimen consisted of three pieces of tissue, the largest of which measured 25 × 10 × 6 mm. in greatest dimensions. The pieces were elliptical and dome-shaped. The largest pieces were covered with a few small blond hairs. The underlying tissue was moderately firm, grayish-white in color, and showed some small streaked areas of hemorrhage.

Fig. 1.—Photograph of infant showing the location and configuration of the tumor prior to operation.



*A.* *B.*

Fig. 2.—*A*, Low power photomicrograph (×40) showing the infiltration of the tumor close up beneath the epithelium and skin appendages. (Masson Stain), *B*, Higher power photomicrograph (×200) showing the plump gemistocytic astrocytes which were quite numerous in the tumor (Hematoxylin and phloxine stain.)

Microscopically the sections showed the overlying covering of thin, well-differentiated, stratified squamous epithelium with some hair follicles, and sweat and sebaceous glands in the papillary layer of the corium. Much of the corium and subcutaneous tissues were replaced by a poorly circumscribed, unencapsulated mass of glial tissue which contained many astrocytes of the gemistocytic type. The matrix of the tumor tissue was a fine feltwork of glial fibers. There were moderately numerous, small, essentially normal blood vessels present. Masson's trichrome stains showed occasional strands of collagenous tissue fibers extending down into the glial tissue and silver stains showed moderately abundant reticulum about the adventitia of the blood vessels running through the tumor. The diagnosis was astrocytic glioma. (See Fig. 2, *A* and *B*.) It should be emphasized that most of the astrocytes were of the gemistocytic type.

Postoperative x-rays were taken of the skull and these showed no defect in the floor of the anterior fossa which would indicate a communication of the tumor with the intracranial contents. The skull was considered normal for a child of her age. The child's postoperative course was uneventful.

SUMMARY

A case of a rare congenital tumor; a nasal glioma of the extranasal type has been presented which seems sufficiently unusual to be worthy of reporting. The various theories as to the origin and nature of these lesions have been discussed in the paper by Hill[6] and others, [1, 2, 5] but it is the belief of the authors that most or probably all of these lesions represent a congenital malformation.

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## Erratum

In the article, "Loeffler's Syndrome With Skin Manifestations," by Drs. Albert M. Jones, and Evelyn B. Ogle, Memphis, Tenn., appearing in the April issue of the JOURNAL OF PEDIATRICS, the first sentence on page 507 should read, "On the second hospital day, the rash showed little change, except in the suprapubic region where there were irregular, confluent, dull red areas of variable size, some approaching 1½ inches in diameter."

# Psychologic Aspects of Pediatrics

## PSYCHOSES IN CHILDREN—A REVIEW

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IN recent years increasingly more attention has been focused on child psychiatry and especially on psychoses in children. This is evidenced by the rapid growth and great development of the American Orthopsychiatric Association, which is largely devoted to the problems of child psychiatry, and more recently by the organization of a separate section within the American Psychiatric Association devoted solely to child psychiatry. To understand the reasons for this trend, it is well to review the development of our present knowledge of psychoses in children.

Medical thinking in regard to psychoses in general was loose and unorganized until almost the turn of the past century. It was not until 1898, when Kraepelin[1] expounded a common denominator by means of which he could classify and describe a large group of psychoses which he termed "dementia praecox," that organization began to appear in our thinking in regard to psychiatric disorders. Even then many years elapsed before much attention was given to the possibility of psychoses in the first decade of life, although as early as 1834, Friedreich made reference to psychoses in childhood. In 1845, Griesinger and Esquirol also mentioned this condition. Greene[3] quoted the latter as holding the opinion that childhood is a period immune from insanity except in those children who have had convulsions or who have had some congenital abnormality. Lutz[2] stated that Emminghaus,[4] in 1887, already realized that since children have illnesses peculiar to themselves, the mental disorders of adult life could not possibly occur in children. Maudsley, on the other hand, felt that all adult psychoses might at times be observed in children. Schonthal,[5] in 1892, reported ten cases of childhood psychoses. He stressed the necessity for distinguishing between immature children and adolescents, if the mental disorders of early life are to be properly understood.

Despite the work published prior to 1900, psychoses in children continued to be considered so rare as to be almost nonexistant and until recently many physicians hesitated to make a diagnosis of psychosis in the preadolescent patient. This situation was caused by several difficulties including: (1) the lack of a uniform definition or accepted criteria for diagnosing psychoses in general; (2) the tendency to overlook symptoms peculiar to psychoses in this age group while at the same time seeking those symptoms characteristic of adult psychoses; and (3) the intellectual inmaturity of the child which made it difficult to establish rapport with him.

In 1905, DeSanctis[6] introduced the term "dementia praecocissima" for those cases occurring in very early life, as opposed to those cases occurring around puberty, and reported several cases occurring as early as the fourth year. Similar reports then appeared in the Swiss, French, Italian, and German literature. In subsequent years, however, dementia praecocissima was shown to include a variety of pathologic conditions including schizophrenia, encephalitides, and other organic brain disease entities. Weygandt[7] and Heller[8] wrote at length on what they termed "dementia infantilis" and expressed views similar to those of DeSanctis.

Kraepelin[1] himself made only brief reference to childhood dementia praecox and stated that in 3.5 per cent of cases in adults, the signs and symptoms could be traced back to early childhood. Bleuler[9] stated that schizophrenia may occur as early as the seventh year.

Raecke[10] (1908) and Vogt[11] (1909) expressed opinions similar to those held today. Bradley[12] stated that Vogt "discusses the problem in a most enlightened fashion. He not only insists that children are properly individuals in whom puberty has not yet appeared (a point still generally neglected by most authors), but also explains certain dementia praecox manifestations peculiar to children in the light of the child's own limited development and special psychological characteristics." In 1910, Strohmayer[13] expressed the opinion that all the psychiatric disorders of adults, with the exception of paranoia vera, arteriosclerotic psychoses, and senile dementia, applied equally well to children.

In 1911, Bleuler[14] introduced the term "schizophrenia" in order to avoid the prognostic implications of "dementia praecox." He stated that the condition "may come to a standstill at any stage and some of its symptoms may clear up to a large extent or altogether, but if it does progress, it leads to dementia of a specific type."

During the next two decades the textbooks of psychiatry treated the question of childhood psychoses relatively lightly. Among the outstanding contributions were those of Voigt[15] (1919), Halberstadt[16] (1926), Homburger[17] (1926), Volokhoff[18] (1929), Fust[19] (1931), Potter[20] (1933), and Simson[21] (1934). In his paper in 1937, Lutz[2] gave a comprehensive review of the literature.

Much of the literature during this period was devoted to a study of the incidence of the functional psychoses among children. Hagen[22] found only one case of psychosis in a child among 72,000 inhabitants. Rhein,[23] in 1914, was able to collect only forty-four case reports of psychoses in children. In reviewing 5,000 consecutive admissions to the Pennsylvania Hospital, Strecker[24] found only eighteen cases of psychoses in children under 15 years of age. As late as 1929, Kasanin[25] stated "in clinics dealing with behavior children—reports of psychoses in children are rare." In 1931, the same author reported that only two or three cases of affective psychoses in children are seen per year out of an average of 1,900 yearly admissions to the Boston Psychopathic Hospital. Kanner, in a series of approximately 1,700 children up to the age of 14 studied at the Harriet Lane Hospital, found only four children considered to be psychotic.

These figures are in sharp contrast to the findings of Lurie, Tietz, and Hertzman[26] at the Child Guidance Home in Cincinnati, Ohio, where an analysis of the first 1,000 cases showed that 2 per cent of the children were definitely psychotic. Bradley,[27] in 1941, reported that out of 251 children admitted because of behavior disorders, there were four children under 16 years of age with definite schizophrenic psychoses.

### SYMPTOMATOLOGY

Around this time, various investigators began to turn their attention to the problem of what constitutes a psychosis in a child, and how psychoses in children differ from those in adults. Among the first to discuss this were Lurie and his associates,[26] who concluded that "the simultaneous occurrence of an abnormal trend in the intellectual, social, and emotional development of a child without an apparent organic basis, may pressage the development of frank psychosis later in life."

Bradley[28] pointed out in 1945, that the term psychosis should not be used to indicate a specific mental disease or disorder in children. "There has, until recently, been a tendency to discuss this subject in child psychiatry by presenting classical descriptions and groupings of adult disorders, and trying to fit certain maladjusted children into these fixed categories." He suggested the definition of psychosis as "a severe mental disturbance or pathological reaction pattern in which all the usual forms of adaptation to life are involved." Or as Hinsie[29] states, "the disorganization of the personality is extensive."

In adults common indications or pathologic symptoms of psychosis are a lack of insight, and the presence of hallucinations and delusions. In children these particular phenomena as deviations from normality are quite unusual, possibly because the immature psyche has not developed capacities which may be disturbed so as to produce these symptoms. It is therefore necessary to use other than conventional criteria in diagnosing a psychosis in childhood.

Bradley also decried the tendency until recently to use the word "child" to cover individuals up to 18 years of age. He suggested that "individuals who have passed their thirteenth birthday, or who show psychological evidences of puberty, be no longer considered children," and noted with satisfaction that current reports have followed this recommendation.

The most common childhood psychosis is schizophrenia. According to Bradley,[28] a schizophrenic psychosis in childhood represents a severe distortion of the entire personality, most conspicuously distinguished by lack of interest in and of voluntary contact with the environment. The patient seems to derive little or no real satisfaction from the ordinary events of life; in contrast to which he appears genuinely interested in and preoccupied with his own thoughts, fantasies, and solitary activities. Individual symptoms may appear in a variety of combinations. No single symptom or group of symptoms is specifically diagnostic. The diagnosis must be made on the total personality picture, past and present. This picture must in its totality portray the child's inability to deal with reality and his retreat into himself."

Bradley and Bowen,[27] in 1941, found that schizophrenic children show various combinations in extreme degrees of certain observable behavior traits. These include seclusiveness, irritability when seclusive activities are interrupted, excessive daydreaming, bizarre, grotesque, externally unmotivated behavior, diminution of personal interests, and preoccupation with interests common to younger children, striking sensitivity to being criticized, and less physical activity than would be anticipated in children of similar age. A common example is seen in simple, monotonous, repetitive play with some object, or quietly rocking back and forth in a sitting or standing position. Disturbances in speech range from mutism to unintelligible chattering. The importance of these speech mannerisms have been emphasized further by Despert.

Some of the most outstanding symptoms of adult schizophrenia were absent in many of the most psychotic children examined by Bradley.[31] Systematized delusions, and hallucinations in particular were conspicuous by their absence.

Bender[32] (1942) felt that schizophrenia should be diagnosed in a positive fashion in children and felt that the factors helping to establish the diagnosis are: (1) true psychotic reactions, (2) a disturbance at every level of adaptive function, (3) a fundamental pattern of withdrawal from reality, and (4) a reliable history of some difficulties in adaptation to persons and to changes in the immediate environment in the earlier years before the psychosis became apparent.

Most reports state that a history of a period early in life entirely free from evidence of mental illness is a fundamental characteristic of schizophrenia in childhood. In contrast to this, Bradley[28] concludes that "the preliminary period of satisfactory adjustment does not seem essential to a diagnosis of schizophrenia."

In 1944, Kanner[33] introduced the term "early infantile autism" to classify certain juvenile psychoses and noted their occurrence as early as in the first two years of life. "The characteristic features consist of a profound withdrawal from contact with people, and obsessive desire for the preservation of sameness, a skillful and even affectionate relation to objects, the retention of an intelligent and pensive physiognomy, and either mutism or the kind of language which does not seem intended to serve the purpose of interpersonal communication. An analysis of this language has revealed a peculiar reversal of pronouns, neologism, metaphors, and apparently irrelevant utterances which become meaningful to the extent to which they can be traced to the patient's experiences and their emotional implications."[35]

That early infantile autism is not an aphasic phenomena related to congenital word deafness is demonstrated by the fact that the latter group responds quickly to gestures and develops warm interpersonal relationships. Kanner[35] stated, "one can hardly speak of an insidious onset of early infantile autisms, except perhaps with reference to the first semester of life. The disturbance is apparent as early as the second half year of life. The infants seem unusually apathetic, do not react to the approach of people, fail to assume an anticipatory posture preparatory to being picked up, and when they are picked up, do not adjust their posture to the person who holds them. They seem happiest when

left alone. Persistent lack of responsiveness raises doubts about the child's hearing acuity. When it becomes obvious that hearing is not impaired, poor test performances lead to the assumption of innate feeble-mindedness. This succession of a first diagnosis of deafness and a second diagnosis of mental deficiency is almost invariably a part of the case histories of autistic children." Despert[36] (1950), has also emphasized the wide variations seen in autistic manifestations.

One is struck by the similarity between many of the diagnostic criteria for infantile autism and for childhood schizophrenia. This question arises: are there any fundamental or basic differences between these two conditions?

Using Bradley's age limitation, many observers have concluded that mania does not occur in children. However, a few cases have been reported at the ages of 11 and 12. Kasanin and Kaufman,[25] and Kasanin[30] in their reviews found few cases of manic depressive psychosis in children. Again, of the cases reported, most occurred between the ages of 14 and 16. Bradley,[28] concluded that "for the present it is best to avoid the diagnosis of manic-depressive psychosis in children."

Psychoses with organic brain disease whether due to trauma, neoplasms, inflammation, or infection are not uncommon in children. In 1942, Lurie and Levy,[37] showed that pertussis in early infancy may be followed by prepsychotic and psychotic states. In 1948, Greenebaum and Lurie,[38] in commenting on the frequency with which encephalitis may complicate any acute infectious disease of childhood, divided the abnormal patterns of behavior which children so affected may exhibit into three groups: (1) simple behavioral disturbances, (2) psychopathic behavior, and (3) psychotic behavior. In their series of seventy-eight cases, twenty-six children presented simple behavioral difficulties, thirty-six showed psychopathic type of behavior, and sixteen were psychotic. Those children who were classified as psychotic showed severe disorganization of cerebral function. They were careless of their personal appearance and slovenly in their habits. Moodiness, crying spells, and irrelevant talk were often noted. Outbursts of screaming and unprovoked laughter were also often present. Occasionally hallucinatory phenomena were in evidence. When thwarted, these children became violent and it was difficult to control them. It was impossible to establish rapport with them. The authors noted that some of the children in this series had previously been diagnosed as schizophrenics.

According to Bradley, psychotic behavior is a not infrequent complication of severe Sydenham's chorea. Characteristic psychotic behavior is rarely reported in epileptic children, but it does occur with frequent and severe grand mal attacks.

In this connection, mention should be made of syphilis as a cause of juvenile psychotic manifestations. Lurie, Greenebaum, and Levy[39] reported eight cases of juvenile paresis in a series of 1,850 children admitted for study at the Child Guidance Home in Cincinnati because of behavioral difficulties.

An interesting controversial issue has been the subject of hallucinations in children. In sharp contrast to the copious literature on hallucinations in adults, scant attention has been paid to the problem of delusions and hallucinations in

children. Even then, most of this work has been done in studies on psychotic children. Various psychologists and psychoanalysts and notably Bernfeld,[40] feel that hallucinations may constitute a normal phenomenon in infants and young children and contend that a hungry infant hallucinates a situation in which gratification takes place. Sherman, Mandel, and Beverly[41] studied a group of children whose intelligence quotients were below 100. They found that "in some children, the hallucinations were simply projections of their mental difficulty, in others a means of compensation or explanation for their difficulty." The psychotic child, they felt, attempts to adjust by means of imagery in much the same way as the normal child uses imagery to gain wish fulfillment.

Despert[42] studied a group of 106 children over a ten-year period at the Payne Whitney Nursery School and was unable to confirm these observations. "It can be emphatically stated that there is no evidence of true hallucinations or delusions either expressed by the children or observed by outsiders at home or at school." She also differentiated between normal and psychotic day-dreaming. In the former group, daydreaming may occur suddenly during play but the child gives evidence of active mentation inwardly turned. In the psychotic child "the body tonus is depressed, the facial expression lacks animation, and there frequently appear some infantile manifestations such as sucking or chewing of the fingers."

The symptomatology varied considerably with the age of the child. Above the tenth-year level "the delusional experiences, including hallucinations are very similar to those of adults, except for their greater simplicity and the total lack of organization and systematization of the delusional content."[42] Despert concluded that delusions frequently represented identification with animals, or were manifestations of regressive patterns of behavior and ideation, with the reappearance of very primitive forms of expression.

The problem of hallucinations and delusions in childhood is of fundamental importance and hence it is essential that more intensive research be employed to further clarify this topic.

## TREATMENT

The treatment of psychotic children presents a difficult challenge which, unfortunately, has not as yet been met. Many remedies, including those which have been successful in adults, have been tried. Various drugs such as Benzedrine, ephedrine, caffeine, and Sodium Amytal have proved to be of little, if any, value.

Shock therapy using insulin, Metrazol, and electroshock either alone or in combination was found to be disappointing by many investigators. Recently, Levy and Southcombe[43] (1950) reported the results in a controlled series of cases of juvenile schizophrenics treated with convulsive therapy as compared to a similar but nontreated group. They found a recovery rate of 12.6 per cent in the juvenile schizophrenic patients who had received various forms of convulsive therapy. This compared with a recovery rate of 16 per cent in the

nontreated group. They concluded that the convulsive therapies do not appear to influence favorably the course of juvenile schizophrenia, in marked contrast to their beneficial effect in cases of adult schizophrenia.

In our opinion, the difference in the therapeutic results in the various forms of schizophrenia evokes another thought. The term schizophrenia, as mentioned before, was introduced into psychiatric nomenclature by Bleuler in 1911. He did this to turn away from the fatal prognostic implication of the term dementia praecox. Today the two terms are used interchangeably. We question the correctness of this usage.

Schizophrenia consists of a number of widely differing syndromes with a multitude of etiological factors ranging from the biochemical, endocrine, genetic, and neurophysiologic to the psychologic. Careful analysis of the schizophrenias permits their differentiation, from the etiological standpoint, into two broad groups. In the one group the etiological factors are primarily somatic and in the other they are primarily psychogenic. The term "dementia praecox" is applicable to the former while the term "schizophrenia" should be reserved for the latter. The prognosis is different in the two forms. It is very grave in dementia praecox and more favorable in schizophrenia. Such a differentiation might explain the differences in results obtained by different clinicians from convulsive shock treatments and various other forms of therapy. Furthermore, limitation of the term schizophrenic to the psychogenetic cases permits of the interpretation of schizophrenic reactions in children as protective reactions and not necessarily as symptoms of a malignant psychosis.

Freeman[44] has recently advocated the use of prefrontal lobotomy in psychotic children, but it is too early to adequately evaluate the results of this radical form of treatment.

Psychotherapy was found to be the most useful therapeutic method by Rappoport[45] as well as by Lourie, Pacella, and Piotrowski.[46] The latter group reported a complete recovery in 20 per cent of their cases. Fabian and Holden[47] (1950), in reporting the results of group psychotherapy in schizophrenic children stated "experiences with the children and parents have been encouraging."

We agree with Kanner[48] that "treatment of childhood schizophrenia is still in the stage of experimentation, but definite trends have emerged which no longer justify an attitude of therapeutic nihilism and prognostic gloom as a conditioned reflex on making the diagnosis of schizophrenia." Bender[49] and Despert[50] likewise believed that the prognosis in juvenile schizophrenia was not as poor as previously reported.

From the material outlined in this article, it can be seen that child psychiatry, and especially the study of psychoses in children, has made rapid strides in the past few decades. In fact, it has reached the position of a subspecialty in the field of psychiatry, and enjoys the same relationship that pediatrics bears to general internal medicine. It now calls for distinct technical skills and knowledge of specific therapeutic techniques that experience and training in adult psychiatry alone can no longer give.

Unfortunately, our management of psychotic children is still archaic. In many respects, it is similar to the manner in which juvenile delinquents and criminals were formerly handled. Until the beginning of the century, juvenile offenders were herded in jail with adult criminals and tried in the same courts. Today such treatment is considered outmoded and barbaric. We pride ourselves, and justly so, on our juvenile courts. However, very few state hospitals for the mentally ill have special facilities for juvenile psychotics. Children committed to these institutions are placed in wards with adult patients and subjected to the same regimen. This anomalous condition should be corrected. The techniques that are applicable to the study and treatment of adult psychiatric condtions are not applicable to juvenile psychotic states. Mentally ill children should have hospitals of their own where techniques applicable to their special needs are available.

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# Clinical Conference

## CONFERENCE AT THE MOUNT SINAI HOSPITAL OF NEW YORK MARCH 24, 1949

By Samuel Karelitz, M.D.
(Horace L. Hodes, Pediatrician-in-Chief)

### INTRODUCTION

Dr. Samuel Karelitz.—For today's presentations I have selected four patients. The first one has Henoch-Schönlein purpura with visceral manifestations and finally renal disease. The second is a known asthmatic child who developed purpura, diffuse vascular disease of the periarteritis nodosa type, and renal involvement. The third is a child with dermatomyositis who has made a remarkable recovery, and the fourth is an extraordinary case of lupus erythematosus disseminatus. The first two patients are hospitalized at present, the latter two patients were in the hospital and have been brought back for this clinic.

It is unusual for us to have such striking examples of the group of erythemas described by Osler. Three of these cases belong to the group of collagen disturbances and all four are currently considered to be due to reactions of hypersensitivity.

### Case 1. Henoch-Schönlein Purpura With Nephritis

Richard M. Ruben, M.D. (Resident Pediatrician).—This 5-year-old white boy had been generally well until the onset of his present illness, seven months ago. At that time, he awoke early in the morning, had four stools within a short time, then began to complain of severe epigastric pain. The stools were described as having been dark, semisolid, but neither black nor grossly bloody. He continued to complain of abdominal pain throughout the day. His appetite was not impaired and no nausea or vomiting was present. Toward the afternoon, he began to complain of aching pain in the left ankle, aggravated by walking. He was observed at this time to have developed a rash on both legs. He was put to bed, but because of continuing abdominal distress, he was brought to the hospital on Sept. 11, 1948, about twelve hours after onset.

On admission, he was found to be a well-nourished and well-developed child appearing neither chronically nor acutely ill. The temperature was 102° F. The most striking finding was the presence of multiple papular and macular, deeply red, erythematous areas over both legs. A few were purpuric in appearance. The lesions varied in size; the largest was about 1 cm. in diameter. They were nontender and did not blanch on pressure. The left ankle appeared slightly swollen and, although tender, there was no limitation of motion. Examination of the ears, nose, and throat was negative except for slightly hypertrophied tonsils. The lungs were clear and the heart, save for a soft musical apical systolic murmur, was normal. The blood pressure was 80/40, and the pulse 125. The

From the Services of Drs. Samuel Karelitz and Jerome L. Kohn of the Department of Pediatrics of the Mount Sinai Hospital, Horace L. Hodes, Chief.

abdomen was soft with the spleen edge palpable one finger below the left costal margin; the liver was not felt. The extremities and genitals were normal.

*Laboratory Findings.*—Laboratory results were as follows: Blood hemoglobin 11.0 Gm.; red blood count 4.6 million; white blood count 11,000; polymorphonuclears 65; lymphocytes 25; monocytes 7; eosinophiles 2; basophiles 1; erythrocyte sedimentation rate 10 mm. per hour (Westergren). Stool *guaiac* was 4 plus. Urine specific gravity was 1.020; alkaline, albumin and sugar were negative; microscopic examination was negative. Nose and throat cultures: *Neisseria catarrhalis.* Stool culture: *Bacillus coli.* Blood culture, negative. Wassermann test was negative. Mantoux tuberculin test was 1 mg. negative. Clotting, bleeding, and prothrombin times all were within normal limits. Tourniquet test was normal. Electrocardiogram was normal.

Until the laboratory reports and further clinical observation had ruled out the possibility of sepsis, the patient was given sulfadiazine (4.5 Gm. daily by mouth for 3 days) and procaine penicillin (300,000 units intramuscularly continued for 2 weeks), without effect upon the continuing eruption. On the second day the eruption was more characteristically purpuric in appearance. The abdominal pain was associated with vomiting and mild acidosis for several days, necessitating the use of parenteral fluids. For the next five to six weeks, the patient was kept in bed. He ate well and was afebrile. He continued to have intermittent attacks of abdominal pain of varying severity, and his stools were consistently positive for occult blood. There were five further major eruptive periods, not related to the abdominal pain, the rash appearing chiefly on the extremities and to a much lesser degree on the trunk. The rash varied from an erythematous papular or nodular type to a purpuric lesion which seldom exceeded 1 cm. in diameter. In the third week, there was a brief transient episode of left scrotal pain, tenderness, and swelling which cleared spontaneously and appeared to have been a vascular disturbance (effusion, hemorrhage, or both) involving the testicle and epididymis.

During the sixth hospital week, examination of the urine which had heretofore been negative revealed an increasing number of red blood cells, 3 to 4 plus albumin, and granular and hyaline casts. The onset of these findings were not associated with fever, headache, or clinical edema although there was a gain of from 2 to 3 pounds during the ensuing two weeks. There had been no preceding upper-respiratory infection. The blood pressure remained as before at 100/60. Save for an evaluation of the erythrocyte sedimentation rate to 40 mm. per hour, the other laboratory findings remained as before, without change in blood count, platelets or bleeding, clotting or prothrombin times. Blood urea nitrogen was 9 mg. per cent.

For the subsequent nine weeks, the patient continued to show numerous red blood cells, varying amounts of albumin, and casts in the urine. At the end of this period, there seemed to be little improvement in the urinary findings. The patient had remained afebrile, uncomplaining, with only one mild new purpuric eruption and no further abdominal pain. The stool guaiac became negative. Blood pressure was unchanged. Blood urea nitrogen remained normal.

In view of the failure of attempts to identify a cause for the disease, either infectious, allergic, or otherwise, and the failure of various types of therapy including antihistaminic drugs (Pyribenzamine, Neo-antergan), vitamins C and K, and rutin, it was decided to observe the child at a convalescent home, and the patient was discharged on Dec. 13, 1948, after fifteen weeks of hospitalization. He was seen several times in follow-up clinic during the next two months and appeared well except for the persistence of mild albuminuria, although microscopic examination of the urine was negative.

He was readmitted on March 21, 1949, because of a sudden attack of abdominal pain, headache, and vomiting. His temperature was 103° F., but the physical examination was generally unrevealing save for mild abdominal tenderness, not well localized. There were no purpuric lesions. Blood pressure was 116/68; fundi were normal; a soft apical systolic murmur was present; electrocardiogram was normal. Total blood protein was 5.3 mg. per cent. Urine examination again showed numerous red blood cells, albumin, and casts of both cellular and granular variety. The erythrocyte sedimentation rate was moderately elevated at 50 mm. per hour. As on the previous admission, there were no abnormalities of the blood elements or the clotting, bleeding or prothrombin times.

The acute episode and the fever subsided rapidly, and the patient was observed for an additional three weeks during which time the erythrocyte sedimentation rate remained elevated and the abnormal urinary findings persisted. Blood urea nitrogen was 10 mg. per cent. Renal concentrating power present to 1.036 specific gravity, and phenol sulfonphthalein excretion test showed 60 per cent excretion within one hour. The patient was again discharged to the follow-up clinic.

In summary, the patient is a 5-year-old boy who, in the course of what seemed to be a characteristic Henoch-Schönlein purpura, developed an acute hemorrhagic nephritis. Although the symptoms and signs of the former subsided, there was a persistence of the urinary abnormalities (albumin, casts, and red blood cells) with an associated elevation of the sedimentation rate, and it seemed a distinct possibility that the patient might go on to a chronic glomerular nephritis.

## DISCUSSION

The vascular lesion involved in the production of the visible skin lesions of Henoch-Schönlein purpura has been described by numerous observors. It consists of an exudation about the capillary or tiny arteriole or venule found in the superficial portion of the corium. The exudate contains polymorphonuclear cells and histiocytes, varying amounts of red blood cells and serum, and occasionally, but not always, eosinophiles. Fibrinoid degeneration of the perivascular collagen is not a feature of the lesion. (The pathologic lesion is the same whether the clinical lesion be an erythema or purpura.)

If it is assumed that the renal lesion is of a similar exudative nature, it would seem logical to expect that the lesion would have the same transient duration it has elsewhere. This has been observed in the transient renal bleeding of the thrombopenic purpuras. In addition, the presence of such a lesion in the

renal parenchyma need not be associated with a rise in the sedimentation rate where there was no rise with the occurrence of lesions in the skin and intestine. In this case, however, the renal lesion persisted, and the sedimentation rate which was normal before the onset of the nephritic episode has since remained elevated. It seems possible, therefore, that the renal lesion may not represent another manifestation of the original purpuric syndrome but rather an associated acute glomerular nephritis. The few cases of nephritis following Henoch-Schönlein purpura that have come to autopsy have shown the lesions of chronic glomerular nephritis. The relationship between the two remains obscure, although it has been postulated that the Henoch-Schönlein purpura may fit with glomerular nephritis in the category of vascular disease consequent on a hypersensitive state.

DR. BASS.—I have seen a very similar case. This child also had purpura, blood in the stool, and ensuing severe nephritis with nitrogen retention and severe hypertension leading to convulsion. This case also started as a mild infection and the patient was treated with sulfa drugs which he had previously been given several times. He then developed a severe purulent otitis media, the drum rupturing within twelve hours, for which he was given a penicillin injection. He immediately became extremely edematous, especially his face and lips. At this time the urine had only a faint trace of albumin. Since this was considered an allergic phenomena he was given an antihistaminic drug. The edema disappeared but the otitis continued. Penicillin was given orally and again there was an immediate angioneurotic edema. The infection yielded to aureomycin, but the patient went on to show all signs of hypertensive encephalopathy with many convulsions and a blood pressure of 130/100 to 172/138. In spite of all forms of therapy this patient died.

A biopsy of one of the hemorrhagic lesions showed definite necrotising arteritis and on autopsy typical periarteritis nodosa.

This case is of interest showing that similar lesions, as in the case of Dr. Reuben, if progressive may lead to definite periarteritis.

QUESTION.—How do you explain the normal sedimentation rate early in the disease and becoming rapid later?

DR. KOHN.—In a hypersensitivity reaction the sedimentation rate varies, being normal at times and rapid at times.

QUESTION.—What is the prognosis?

DR. KOHN.—I believe that his prognosis is favorable unless his nephritis becomes chronic.

### Case 2. Periarteritis Nodosa in an 11-Year-Old Boy

DR. BENNETT GEMSON (Resident Pediatrician).—An 11-year-old Puerto Rican boy was admitted to the Pediatric Service of the Mount Sinai Hospital on Nov. 5, 1948, because of abdominal pain for five days. Ten months before admission he developed bronchial asthma for which he was treated in the Allergy Clinic. In the six months before admission he lost 12 pounds in weight. Two months before admission he began to complain of weakness and fatigue. Five days before admission he developed moderately severe midabdominal pain, worse on eating, but also occurring at night while in bed. There was no nausea, vomit-

ing, diarrhea, or fever. Bowel movements were normal. There was no chest pain, cough, dyspnea, chill, or change in the color of the urine or stool. There was no bleeding from nose or gums and no muscle pain.

The family history was noncontributory. The past history revealed that the patient had been hospitalized for two weeks at the age of 4 years because of hematuria of unknown cause. He had been previously admitted for a fracture of the left forearm at 9 years.

Physical examination on admission revealed a thin, fairly developed 11-year-old Puerto Rican boy with prominent ribs and bony shoulders, appearing mildly chronically ill and in no acute distress. Temperature was 100.2° F. Pulse rate was 100. Blood pressure was 100/70. There were several papular crusted lesions, 1 mm. to 1.5 cm. in diameter on the knees and elbows. There were splinter hemorrhages of the second and fifth nailbeds of the right hand and of the second to fourth nailbeds of the left hand. There were a few small pinhead-sized red lesions on the right-lower conjunctival sac and one such lesion on the left lower conjunctival sac. Both nasal turbinates were slightly hypertrophied and somewhat pale. Examination of the ears, mouth, and throat were negative. There was slight, generalized glandular enlargement, especially anterior cervical, axillary, and inguinal with pea to bean-sized, firm, discrete nodes. There was an almond-sized, slightly tender right femoral node. The chest was hyperresonant to percussion. Examination of the heart and lungs was negative. The abdomen was soft and flat, and there were no masses, tenderness, rigidity, or spasm. There were oval, erythematous macules, 2-5 mm. in diameter, moderately tender, on the balls of both feet.

*Laboratory Findings.*—Laboratory findings on admission were: hemoglobin 11.5 Gm.; white blood cells 23,700; polymorphonuclear leucocytes 39 per cent; nonsegmented polymorphonuclear leucocytes 3 per cent; lymphocytes 6 per cent; monocytes 3 per cent; eosinophiles 49 per cent. The urine was negative for albumin and contained from 2 to 3 red blood cells and 1 to 2 white blood cells per high power field of uncentrifuged urine. The erythrocyte sedimentation (Westergren) rate was 85 mm. per hour. Schick and Mantoux tests were negative. Bleeding time, clotting time, and clot retraction were normal. The heterophile agglutination titer was 1:14. The Trichinella precipitin test was positive in a dilution of 1:1280. The stool was negative for ova, parasites, and blood. The total serum protein was 7 Gm. with 3.6 Gm. of albumin and 3.4 Gm. of globulin. Cephalin flocculation was 2 plus. Serum cholesterol was 540 mg. per cent with an ester fraction of 180 mg. per cent. (Normal range in this hospital is up to 350 mg. for cholesterol and up to 250 mg. for esters.) A blood culture on admission was reported as positive for a gram-negative rod of the *Hemophylus influenzae* group. The organism was susceptible to 10 units of penicillin and 1 unit of streptomycin per cubic centimeter, and resistant to 100 mg. per cent of sulfadiazine. X-ray of the chest showed an irregularity of the pulmonary markings of the right-upper and right-lower lobes with adhesions of the pleura between the lobe. The appearance was suggestive of a nonspecific inflammatory disease of considerable duration.

Because of the history of allergic phenomena, abdominal pain, and high eosinophilia, a diagnosis of diffuse vascular disease, i.e., periarteritis nodosa, was entertained on admission. Parasitic infestation, trichinosis, infectious mononucleosis, Hodgkin's disease, and chronic sepsis were also considered. Repeated examinations of the stool for ova and parasites were negative. Biopsy of the left deltoid muscle showed interstitial myositis with eosinophilic infiltration. Because of the positive blood culture, the patient was treated with intramuscular streptomycin, receiving 2 Gm. in divided doses daily for three days, followed by 1 Gm. a day for a total of 3 weeks. After 2 weeks on streptomycin, a blood culture was negative and remained so. The clinical picture of persistent abdominal pain, rapid sedimentation rate, leucocytosis of 25-40,000, and eosinophilia of from 50 to 85 per cent persisted, although the temperature returned to normal early in the second week. At the end of the third week numerous small firm nodules were palpated in the scalp. Biopsy of one of these nodules showed subcutaneous tissue containing a core of necrotic tissue with peripherally arranged palisaded epithelioid cells and a vascularized inflammatory zone containing many eosinophiles. The impression was "connective tissue injury as seen in hypersensitivity states." The blood pressure, normal on admission, gradually rose to 120/90 by the end of the fourth week. The eyegrounds, negative on admission, began to show tortuosity of the arterioles, increased light reflex, and moderate compression of veins, interpreted as due to retinal hypertension. Electrocardiogram showed sinus tachycardia, and a tendency to right axis deviation, a flat $T_2$, and an inverted $T_3$, interpreted as being due to myocardial involvement. During the sixth week, the patient complained of numbness in the right hand. Neurological examination disclosed a loss of sensation to touch, pressure, and pain over the distribution of the median nerve. At this time numerous split pea-sized tender nodules were palpated along the medial aspect of both arms, and a crop of tender hemorrhagic lesions appeared on the balls of both feet. The urine at this time showed a trace of albumin, occasional red blood cells, and hyaline casts.

The patient was discharged to receive physiotherapy to his right hand. At time of discharge, he presented the picture of progressive diffuse vascular disease with gradually increasing hypertension and multiple sites of peripheral vascular involvement.

The patient was readmitted on April 6, 1949, two and one-half months after discharge, because of a severe asthmatic attack. He had been relatively well since discharge save for generalized weakness and poor appetite.

Physical examination on this admission revealed a pale, thin, chronically ill boy, appearing more wasted than previously. His weight was 50 pounds, 2 ounces, as compared to 53 pounds, 8 ounces, at time of discharge. The blood pressure was 170/120. The pulse rate was 160. Respirations were rapid and noisy with an audible wheeze. The ocular fundi showed slightly increased hypertensive retinopathy with a linear hemorrhage adjacent to the disc on the left in addition to the previous findings. The chest was hyperresonant with diffuse asthmatic wheezes and prolonged expiration. There was a tachycardia with sounds of fair quality, and no murmurs. The liver was 2 cm. below the

costal margin. The abdomen was otherwise negative. There were small nodules along the course of both brachial arteries. Neurological examination revealed decreased sensation to pain and temperature over the distribution of the right median nerve with atrophy and weakness of the right thenar muscles and the flexors of the second and fourth fingers of the right hand. There was impaired sensation over the distribution of the right lateral femoral cutaneous nerve. The scalp nodules were smaller than on the first admission. The skin was negative.

*Laboratory Findings.*—Laboratory findings were: white blood cells 10,500 with only one eosinophile on admission. The hemoglobin was 14 Gm. The urine showed 1 plus albuminuria and occasional red blood cells on microscopic examination. The erythrocyte sedimentation rate was 96 mm. per hour. The blood urea nitrogen was 9 mg. per cent. The total protein was 8.4 Gm. with albumin 3.6 Gm. and globulin 4.8 Gm. The serum cholesterol was 200 mg. per cent with esters 150. Renal function tests showed a phenolsulfonphthalein excretion of 60 per cent in two hours, and a maximum concentration of 1.024 on concentration test. Chest film showed emphysema and the infiltration previously noted.

The patient's asthma was rapidly controlled. His blood pressure fell from a maximum of 180/160 on the second day to levels of 138/104. His eosinophile count subsequently rose to 28 per cent. The erythrocyte sedimentation rate fell to normal by the fourth week. He was relatively well during the second week of hospitalization, and by the end of this time had gained 2 pounds, 8 ounces. Subsequently, he developed almost daily asthmatic attacks which were controlled with aminophylline suppositories. He received physiotherapy to his right hand. He was discharged to convalescence after four and one-half weeks of hospitalization.

SUMMARY.—This was an 11-year-old Puerto Rican boy with an asthmatic history, with one episode of renal bleeding, who developed signs and symptoms of a systemic disease two months before his first admission. He entered initially with an *Hemophylus influenzae* sepsis which responded to streptomycin therapy. He went on to develop hypertension, retinal changes, nodules of the scalp and peripheral vessels, eosinophilia, peripheral neuritis, and evidence of renal damage, presenting a picture of diffuse vascular disease (periarteritis nodosa).

## DISCUSSION

Periarteritis Nodosa is a rare disease in infancy and childhood, only forty-four cases having been reported up to 1947.

The work of Rich and his co-workers indicates that the disease may be a manifestation of hypersensitivity. The usual symptoms are fever, weakness, and vague pains in the arms, legs, or abdomen. Subcutaneous nodules, nephritic involvement, anemia, leucocytosis, eosinophilia, nervous system involvement (particularly peripheral neuritis), and hypertension are common findings. There is no specific treatment. The prognosis is poor, the mortality being over 90 per cent, although patients may live for several years after the diagnosis is made. Of interest in this case were the asthmatic history, the initial sepsis with *Hemophylus*

*influenzae*, the high eosinophilia, and the regression of the numerous scalp nodules originally present.

QUESTION.—Since you have no definite histologic evidence of periarteritis nodosa how can you make that diagnosis?

DR. KARELITZ.—Although there were no histologic demonstrations of arteritis the patient fulfills all the clinical criteria of the disease. The skin eruption, the nodules along the brachial artery, the subcutaneous nodules, the peripheral neuritis, the hypertension, and the renal involvement are all absolutely characteristics of the disease. Add to this the allergic manifestations and I believe we have a complete picture of the condition.

*Comment by* DR. KARELITZ.—Dr. Gemson's case seems to be a bridge between the case of purpura presented by Dr. Reuben and the case described by Dr. Bass.

### Case 3. Dermatomyositis

DR. ROBERT D. LONDON (Resident Pediatrician).—On July 23, 1947, a 5½-year-old white male child was admitted to the Mount Sinai Hospital with a history of illness of nine weeks' duration characterized by a skin rash, voice change, and painful swelling of the extremities. His previous history and family history bore no apparent relationship to this recent illness.

About nine weeks prior to admission he had contracted an upper-respiratory infection with a coryza that lasted for about two weeks. He was treated with aspirin and Neo-Synephrin nose drops. About one week later, he developed a sore throat and hoarseness of the voice with a temperature rise to 100.3° F. The fever persisted only one day. At that time his mother noted a flush of the skin of his face and neck, and that he became fatigued very readily. She ascribed the flush to sunburn. However, while convalescing from this illness, it was noted that his voice did not resume its normal character, that his gait became marked by short steps, and that the flush persisted. Because of these changes, his doctor was consulted who felt the child had a laryngitis and sunburn and prescribed a course of sulfonamides for four days. The child was afebrile prior to and during this therapy. There was no remission of any symptoms after this therapy and the child had now developed red, swollen, and tender gums. A consultant at that time confirmed the previous physician's impression in regard to the skin and larynx and suggested the diagnosis of rheumatic fever because of tachycardia. An erythrocyte sedimentation rate, blood count, and urinalysis were done and found to be normal. Despite this, he was put to bed for a week and treated with salicylates.

During this period he continued afebrile and was cheerful, but developed a nasal voice and occasionally expelled fluid through the nose while drinking. Re-examination after this time disclosed no change in the patient's condition. The oral lesions were then treated with penicillin troches. Within two days after this rest period he developed pain and puffiness of the left arm. A repeat blood count, urine, and erythrocyte sedimentation rate were again normal. Because of this persistent and progressive symptomatology, he was hospitalized at another hospital. A blood count, urinalysis, bone marrow aspiration, electrocardiogram and spinal fluid examination were all normal. The erythrocyte

sedimentation rate was 34 mm. per hour. Biopsies were taken from the skin of the right cervical region and sternomastoid muscle as well as from the skin of the right thigh and quadriceps muscle. These demonstrated extensive muscle degeneration with marked cellular and interstitial edema. Loss of striation with scattered collection of lymphocytes and mononuclear cells were present. The skin showed thinning and degenerative staining reactions but no other significant changes. On the basis of the clinical picture and biopsy findings the diagnosis of dermatomyositis was made. Therapy in this institution was confined to a four-day course of penicillin.

Following discharge from that hospital, his oral lesions healed and the rash and muscle pain subsided, but he became progressively weaker and found it difficult to raise his arms and impossible to sit without support. Thus, one week later, he was admitted to the service of Dr. Karelitz at the Mount Sinai Hospital.

Physical examination revealed the following abnormal and significant findings. He had a slight facial erythema and edema. The skin of the arms, thighs, and face felt brawny and semi-indurated. Pressure on the dorsum of the hands produced pitting. The apical impulse of the heart was in the fifth left intercostal space just beyond the nipple line. No thrill was palpable. A soft systolic murmur could be heard at the apex and along the left border of the sternum. It was not transmitted. Blood pressures were 140/76 in both arms and 140-147/82-84 in the legs. The ocular fundi showed several small hemorrhagic areas with adjacent gray-white patches that resembled lymph extravasation rather than scarring. The nerve heads were pallid but felt to be within normal limits. Neurological examination disclosed no unusual findings except generalized weakness and paralysis of the soft palate.

In view of the history of onset of dermatitis edema, and myositis, and the corroborating biopsy evidence of skin and muscle degeneration, the diagnosis of dermatomyositis seemed most tenable.

This second period of hospitalization continued for thirty-three days. During that period he remained afebrile, and his general condition improved moderately. He became more cheerful, experienced less pain, and achieved a wider range of motion of his extremities. Repeated examination of the fundi showed resorption of some hemorrhages and the occurrence of fresh ones. The edema of his skin remained stationary. Repeated blood pressures produced lower readings and just prior to discharge it was recorded at 108/70. No particular therapy except Pyribenzamine 50 mg. four times daily was given. It had no apparent effect after a three-week course.

Mantoux and Schick tests were negative. Erythrocyte sedimentation rate, repeated urinalyses, and blood counts showed no abnormalities. X-ray examination of the chest and skull were within normal limits. There was no detectable titer of serum antifibrinolysin.

Since discharge from the hospital, he has been seen frequently and has made a slow but progressive improvement. He now walks and runs and is able to attend school. He has gained about 3½ pounds. He has received Pyribenzamine, Prostigmine, and vitamin E in separate courses. The boy improved but

it was difficult to evaluate to what degree, if any, the improvement was ascribable to these agents. Physiotherapy, whirlpool baths, and massage, have been used continuously with beneficial effect. His ocular fundi became normal in about three weeks and have remained so. The systolic murmur has disappeared and recurred at varying times.

## DISCUSSION

The diagnostic term dermatomyositis is applicable to any disorder in which there is an inflammation of the muscles and fascia associated with a skin rash. The etiology is not known and the disease has been described as following sore throats, measles, pertussis, food poisoning, gastrointestinal disorders, and pregnancy. A dermatotropic and myotropic toxin has been assumed by some. Others regard it as a hypersensitive state of the skin and muscles to the circulating antigen of a bacterial product. There are no characteristic clinical findings except those invloving the skin and muscles. The symptomatology is diverse and dependent upon the acuteness and extent of involvement. There are no confirmatory diagnostic procedures except skin and muscle biopsy. The blood count and urinalysis are normal. Eosinophilia is the exception. The erythrocyte sedimentation rate may be normal or slightly elevated. The basal metabolic rate is normal or elevated. Blood chemistries are normal. There may be a creatinuria which is considered to be indicative of muscle degeneration rather than a specific metabolic derangement.

The finding of retinal hemorrhages and perivascular exudation as was seen in this child is not frequent but has been noted previously.

The differential diagnosis includes trichinosis, rheumatic fever, avitaminosis, scleroderma, poliomyelitis, polyneuritis, and myxedema.

The prognosis is a guarded one, for mortality due to intercurrent infection, decubitus lesions, and involvement of the muscles of deglutition is frequent. The severity of the initial process seems to bear no relationship to the outcome of the disease.

DR. KARELITZ.—Dermatomyositis is a chronic disease in contrast to polymyositis which is usually acute, associated with multiple muscle abscesses or collections of polymorphonuclear leucocytes and sepsis. As in this case presented, rheumatism or poliomyelitis are commonly mistakenly diagnosed. The pain when carefully observed is muscular and not arthralgic, any paralysis if present is associated with edema and induration rather than nerve damage. The rash may vary from an erythema to lupuslike lesions. It may be morbilliform, purpuric, or scarlatiniform, or in some combination of these various rashes together or in sequence. I have seen all of these in various cases of dermatomyositis. Mucous lesions are often present when the disease is referred to as dermatomucomyositis. Like the muscles, the fascia and skin are usually involved. It is one of the collagen diseases, a kindred condition to lupus erythematosis, scleroderma, and periarteritis nodosa. Recovery may be expected in many cases with modern therapy, provided the heart is not too seriously involved. Of all the therapeutic agents given to this patient only physiotherapy seemed to have an immediate beneficial effect. Whether vitamin E,

other vitamins, or antihistamines, or Prostigmine, were beneficial is difficult to evaluate. The use of penicillin with every intercurrent infection was of great importance, since it cured the patient of infections which in the past were disastrous to such a child.

I have seen the whitish patches observed in the ocular fundi of this boy only once before in a child who had had a fractured skull. These extravasations were presumed to be due to ruptured lymphatics, but I am now told that lymphatics do not occur in the fundi. These lesions must therefore be extravasations of plasma. Dr. Jack Goldsmith had seen similar ophthalmoscopic findings twice in American soldiers both afflicted with dermatomyositis. I can not help raising the question whether the C virus of Daldorff which causes a clinical picture resembling that of poliomyelitis but produces muscle changes similar to those recorded in this patient might be responsible for this disease.

**Case 4. Lupus Erythematosus Disseminatus**

DR. N. SCHIFRIN (Assistant Resident Pediatrician).—This 8-year-old Jewish female child had been well until the early part of 1947, when she incurred a severe sunburn of the face while vacationing in Florida. Most of the burned area healed; however, a reddish, blotchy eruption persisted over the cheeks. Soon after returning to New York City, pallor, listlessness, and sustained temperature elevation were noted. These signs and symptoms continued and were suspected of being due to leucemia. The patient was therefore admitted to the Mount Sinai Hospital on June 20, 1947, for the first time.

Physical examination revealed a very sick, feverish child. She was anemic and had a moderate lymphadenopathy, hepatosplenomegaly, and erythematous, blotchy eruption over the cheeks, and a mild arthritis of both knees. A soft, systolic, apical murmur was heard. The white blood cell count was 3,200 with a moderate shift to the left, 52 per cent polymorphonuclears, 11 per cent nonsegmented, 30 per cent lymphocytes, 1 per cent myelocytes, 1 per cent eosinophiles, 5 per cent monocytes, and 1 per cent reticulocytes. The hemoglobin was 4.5 Gm. per 100 c.c. of blood, and the red blood cell count was 1.5 million. The peripheral blood smear revealed many spherocytes and the sternal marrow examination revealed normoblastosis and a marked reticulocytosis. The diagnosis of hemolytic anemia was entertained by the hematologist, but to some of the pediatricians the rash, leucopenia, and arthritis suggested lupus erythematosus disseminatus. The investigation of the patient's blood revealed a cold agglutinin titer of 1:32 and in addition an autoantibody in the circulating blood which was effective at 37° C. and which agglutinated not only her own cells, but other compatible red blood cells. The autoantibody was not of the usual type and could not be classified. The Coombs test was positive, 3 plus. The blood Wassermann was negative. Red blood cell fragility began at 0.64 and was complete at 0.24° C. Transfusions provided only temporary relief. The patient hemolized her blood so rapidly that a splenectomy was performed on July 24, 1947, in the hope that this might stop the hemolytic process. She improved thereafter and was permitted to go home to be observed there. The spleen showed no significant changes except for considerable congestion and very rare medullary erythropoiesis.

During the five months after splenectomy the patient was readmitted to the Mount Sinai Hospital three times; the first of these for a transfusion and the next two, her third and fourth admissions, were for exacerbations of her rash, fever, and hemolytic process. One exacerbation followed a day of sunbathing. While in the hospital during her second, third, and fourth admissions, the following was noted: The arthritic symptoms formerly involving only the knees had spread to the elbows and several cervical joints, and had increased to the point of ankylosis. The blotchy eruption over both cheeks now extended over the upper lip and was characterized by telangiectasia, follicular hyperkeratosis, and atrophy. There were petechialike lesions on the finger tips and mild clubbing of the fingers and toes. The blood pressure was always normal. Hepatomegaly persisted. Transient eye ground changes were noted. These included tortuosity of the vessels and hemorrhages in the areas around the discs. Bilateral ankle clonus developed and a left Babinski reflex was elicited. The systolic murmur was unchanged.

At home she became progressively weaker, the fever persisted, and she began to cough. She was therefore readmitted to Mount Sinai Hospital on Feb. 16, 1948, her fifth and last admission to this hospital. During this hospital admission she developed cardiac enlargement and transient pleural and pericardial effusions. The leucopenia persisted. Albuminuria developed and, for a short time, red blood cells and varied types of casts were noted in the urine. The Coombs and cold agglutinin titers were negative and the patient now maintained her hemoglobin at about 11 Gm. with one transfusion per month. The blood total protein which had ranged between 6.5 and 7.5 Gm. per 100 c.c. of blood with an albumin globulin ration of approximately 1:1 had risen to 9.4 Gm. per 100 c.c. with albumin of 3.5 Gm. and the globulin fraction 5.9 Gm.

In spite of sulfonamide and penicillin therapy the patient ran a persistent temperature elevation which subsided spontaneously during the latter part of her hospital stay. A twelve-day course of paraaminobenzoic acid, 12 Gm. daily by mouth, was started without any effect on the febrile course or upon the condition of the patient. A course of vitamin C, 300 mg. daily by mouth was given for twenty-one days to no avail. A course of rutin, 100 mg. three times a day for three weeks was of no benefit. The patient gradually improved and was discharged on May 10, 1948, and was to be followed by Dr. Nathan Rosenthal and Dr. Samuel Karelitz.

In summary, this is a case of lupus erythematosus disseminatus complicated by an acquired hemolytic anemia for which a splenectomy was performed with moderate relief. Lupus erythematosus disseminatus was suspected because of the rash (exacerbation after exposure to sunlight), the arthritic complaints, and the leucopenia. While under observation the rash on the face changed from a blotchy, erythematous eruption to one characterized by telangiectasis, follicular hyperkeratosis, and atrophy. In addition, a transient petechialike eruption was present over the finger tips. A pericardial and pleural effusion developed. Persistent albuminuria and a transient episode of formed urinary elements were also noted. She never developed hypertension or eosinophilia.

Lupus erythematosus disseminatus is a diffuse collagen disease with a special predilection for young girls and with characteristic pathologic changes primarily in the endothelium-lined structures, capillaries, small arteries and veins, the endocardium, and the synovial and serous membranes. The constant site of injury lies in the connective tissues of the body. The etiology of this condition is unknown, but the most popular concept is that a reaction of hypersensitivity to some infectious process is probably responsible for the disease.

Characteristically, the patient runs a prolonged irregular remittent fever with recurrent involvement of the synovial or serous membranes. There is depression of bone marrow function with leucopenia, moderate hypochromic anemia, and thrombopenia. In the advanced stages clinical evidences of vascular alterations in the skin, producing the characteristic butterfly rash over the malar eminences and bridge of the nose, in the fundi, producing perivascular hemorrhages and scattered fluffy exudates, in the kidneys, producing albuminuria and hematuria, and in other viscera. The heart may be involved with endocarditis of the indeterminate or Libman-Sacks variety.

Most sufferers from this disease ultimately die. Death is due to toxemia of the disease, to renal insufficiency, or to intercurrent infection. No method of treatment up to this time has been of any value.

*Comment by* DR. KARELITZ.*—I saw this child in my office on several occasions between June 29, 1948, and May 18, 1949. She maintained a hemoglobin between 9 and 11 Gm. and a white blood cell count between 4,500 and 7,500. Her hair was thin and sparse, the rash on the face persisted. She walked stooped over, with legs spread with her knees in partial flexion. She was dyspneic and slightly cyanotic and the heart seemed large to the left on fluoroscopy. She had developed some clubbing of the fingers. The blood pressure remained between 88-98 systolic and 60-70 diastolic. Her fundi remained unchanged. The urinary findings had increased so that a 2-plus albumin, numerous hyalin, some cellular, and few granular casts, and few white blood cells and red blood cells were always in the urine. Various vitamins and antihistaminics were given in full dosage without any demonstrable effect. (Some time after demonstrating this patient at the clinical conference I attempted to obtain cortisone without success.)

In October, 1949, cortisone was obtained for this child because several adults with lupus erythematosus disseminatus had already been treated by Dr. G. Baehr with promising results. However, I learned that it was too late since our patient had died at the New York Hospital.

Through the courtesy of Dr. Samuel Z. Levine, Pediatrician, and Dr. G. W. Richter of the Pathology Department of Cornell University Medical School I am able to give you the continued follow-up including the pathologic findings of the autopsy.

She had become sicker and was admitted to the New York Hospital, Feb. 14, 1949. Her condition was similar to that above noted except that her clinical findings had become exaggerated. The Coombs test and cold agglutin titer were negative. A low blood calcium 7.6 mg. per 100 c.c. was noted. X-rays of

*Addendum to Conference report.

the long bones in the upper and lower extremities failed to reveal any abnormality. On February 21, while in a bed next to a window on a sunny day, she developed a mild recurrence of the butterfly rash over the bridge of the nose and cheeks.

On February 24, a biopsy of the skin and a lymph node in the right axilla was performed and reported as "lymph node is enlarged and crowded with lymphocytes and contains follicles with ill-defined germinal centers. At the margin of the muscle and adherent fat there are areas of fibrous tissue infiltrated with lymphocytes and large mononuclear cells. Much of the collagen appears acidophilic homogeneous and swollen." These findings were considered compatible with the diagnosis of lupus erythematosus disseminatus, but were not diagnostic. During most of the patient's hospital stay she ran a low grade fever. Urine culture was positive for *Pseudomonas aeruginosa* and microscopic examination of the urine revealed many white blood cells. Chloromycetin, 0.25 Gm. by mouth every eight hours, was given for seven days. At the end of this time the pyuria had cleared but bacilluria persisted. She was discharged after three weeks of hospitalization.

On Oct. 21, 1949, she was readmitted to New York Hospital because of severe dyspnea and pains in her bones. She was orthopneic and cyanotic and extremely dyspneic on admission. The neck veins were distended and pulsated. They filled from below. Fine râles were heard at the right base posteriorly. A loud systolic murmur was heard over the entire precordium and gallop rhythm was present. The temperature curve was of the spiking septic type, but blood culture was negative. Her general condition deteriorated rapidly. She convulsed on the seventh hospital day and lapsed into coma. She died on Oct. 30, 1949, the ninth hospital day. Post mortem blood culture was positive for *Ps. aeruginosa* and spinal fluid culture post mortem was also positive for this organism.

*Post Mortem Findings.*—Disseminated lupus erythematosus with Libman-Sacks endocarditis, pericarditis, and pleuritis with effusion: The heart weighs 240 grams (normal 130 grams). At the closing edges of the leaflets of the tricuspid valve there are numerous tiny, light brown, firm, verrucous vegetations. One of these extends along one of the chordae tendineae down to the papillary muscle. It measures 4 mm. in length. In addition there is fibrous thickening in the mural endocardium of the right ventricle. Similar vegetations are seen at the closing edges of the mitral valve and one of the papillary muscles is partly replaced by calcific yellow material. There is also fibrous thickening underneath the left auricular and ventricular endocardium. There are extensive fibrous adhesions between the visceral and parietal pericardium and here and there a hemorrhagic and fibrinous exudate is present on the epicardium over the ventricles. There is an estimated 300-400 c.c. of serosanguinous fluid in each of the pleural cavities. There are numerous fibrous adhesions between the visceral and parietal pleura on both sides, and parts of the visceral pleura are covered by fibrinous exudate.

Acute bacterial endocarditis: There is a friable, red and yellow vegetation upon the anterior and median leaflets of the aortic valve. It measures 12 mm.

× 9 mm. × 5 mm. Smear preparations of this vegetation contain gram-positive cocci and gram-negative bacilli. The latter are also obtained from cultures of portions of the vegetation.

Subacute nephritis: The right kidney weighs 110 grams. The left 100 grams (normal combined weight is 150 gm.). Their capsules are somewhat adherent, and their congested external surfaces show numerous fairly firm, yellow-gray, slightly nodular areas, up to 6 mm.

Cardiac hypertrophy: The heart weighs 240 grams (normal 130 grams). The wall of the left ventricle measures 12 cm. in thickness.

Hepatomegaly: The liver weighs 1130 grams (normal 710 grams). Its cut surfaces are of a yellow color and are firm.

Generalized enlargement of the lymph nodes. There are many enlarged mediastinal and abdominal lymph nodes. Some are pale brown and firm, while others are mottled yellow and red.

Accessory findings: Surgical absence of the spleen: (A splenectomy was performed in 1947 because of hemolytic anemia. Clinical history.)

Cholecystitis with cholelithiasis: There are three black and green stones within the gall bladder, the largest measuring 17 mm. in diameter. The wall of the gall bladder is considerably thickened, and its mucosal surface is roughened.

## DISCUSSION

DR. JOSEPH HARKAVY.—The cases under discussion: lupus erythematosus, dermatomyositis, periarteritis nodosa, and Henoch-Schönlein purpura with nephritis, present certain common features referable to disease of the collagen system, the pathogenesis of which is regarded by a number of investigators to be dependent upon an allergic mechanism. This opinion is based to a large extent on the similarities in the histologic evidence of fibrinoid necrosis and periarteritis nodosalike lesions in disseminated lupus erythematosus and dermatomyositis on the one hand, and on the other, the fibrinoid degeneration in blood vessels in rheumatic fever, periarteritis nodosa, scleroderma, and experimentally produced vascular lesions as reported by Garlach, Klinge, Rich and Gregory, and others. There are those who disagree that similar morphologic changes imply a common pathogenesis. Klemperer and Baehr, for example, do not believe that lupus erythematosus and scleroderma belong to the more clearly defined hypersensitive states such as periarteritis nodosa or serum sickness, because of the absence of any clear-cut evidence of allergy. Yet it is difficult to deny altogether that no allergic component exists in lupus erythematosus. The frequent manifestations of photosensitivity of the skin in the history of patients with lupus erythematosus indicated also in the case under discussion, cannot be regarded as merely coincidental. That sensitivity to ultraviolet light in constitutionally predisposed individuals falls into the category of that poorly understood, though generally recognized syndrome of physical allergy, is a fact. In about one-half of their cases of lupus erythematosus, Ludy and Corson demonstrated hematoporphyrinemia and porphyrinuria which they attribute to light sensitivity. Secondary bacterial invasion leading to subacute bacterial endocarditis in such a light-sensitive individual, as reported in this case, may be

analogous to the bacteral endocarditis so commonly seen in rheumatic disease in which a basic allergy to the streptococcus has been postulated. Fox describes a case which followed serum sickness.

That allergy has been considered by some to play a role in the development of dermatomyositis is based on the fact that there is no specific single etiological factor responsible for this condition. It has been seen to follow a number of exciting agents in the nature of infections such as measles, pertussis, gastrointestinal disease, pregnancy, and even exposure to lead. According to Fahr, the coincidence of hematoporphyrinemia and arterial lesions in lead workers, who have been known to develop dermatomyositis, suggest that lead, similar to bacterial infection, or perhaps autoantigens in cases following pregnancy, may also act as a sensitizing agent. In the case reported herewith there is a definite antecedent history of upper-respiratory infection and sore throat, both of which could have been a source of sensitization in the precipitation of reactions in this patient's shock tissues such as the muscles, fascia, and skin, and give rise to the dermatomyositis. The conversion of dermatomyositis into systemic lupus erythematosus has also been described by Keil and others.

In the pathogenesis of Henoch's purpura there is a good deal of clinical evidence that allergy to bacteria, foods, and drugs play important roles. Eyerman, Hampton, and others, have described this syndrome in cases of food allergy. Kern records a case in which allergy to onion was responsible for renal insufficiency followed by uremia and death. The possibility that in this case the purpura, joint manifestations, and the glomerular nephritis may represent hyperergic vascular reactions in different shock tissues precipitated by bacterial infection and the sulpha drugs which the patient received in the course of treatment, cannot be ruled out.

In the case of periarteritis nodosa above described, the stigmata of allergy were indicated in the following presenting symptoms: bronchial asthma; the presence of pulmonary infiltrations, which in our experience have been shown to be due to hyperergic reactions in the pulmonary vessels and associated structures; and the marked eosinophilia, ranging between 50 and 85 per cent. This was supported by the biopsy of a nodule which showed "connective tissue injury seen in hypersensitivity states." Out of 300 cases of periarteritis nodosa reported in the literature, 25 per cent showed various forms of allergy, 18 per cent of these patients had bronchial asthma.

The possible sensitizing factors in this case may have been a series of antecedent bacterial infections noted in the past history together with the intercurrent influenza bacillus bacteremia present on admission. Thus, a previous infection may have been responsible for the hematuria at the age of 4 years, which may have indicated an attack of acute glomerular nephritis. Later infections could have precipitated the bronchial asthma and the more generalized reactions in various shock tissues manifested by this patient. In a group of seventeen cases which have been observed by us in the past ten years, bacterial allergy played a most prominent role in the development of the hyperergic vascular disease. Clinically, as well as experimentally, a large array of sensitizing agents have been implicated in the etiology of periarteritis nodosa.

In addition to various bacteria, foreign sera, drugs of the sulfa group, iodine, Dilantin Sodium, and other agents have been described. In seven of the cases studied by us, the vascular reactions were reversible, just as in this patient. These individuals became completely well. Other patients with periarteritis nodosa who went on to a state of remission and remained well are reported in the literature. In the patients who recovered the heart and kidneys were as a rule not involved. Ten of our patients died. In these patients the hyperergic vascular disease progressed either because the sensitizing factor was unknown or because it was not, or could not be eliminated. The cause of death was either cardiac and/or renal failure due to severe involvement of the heart or kidneys in the hyperergic vascular process. The prognosis is therefore dependent to a large extent upon the condition of these two vital organs.

# Comments on Current Literature

## STREPTOCOCCAL ENZYMATIC DÉBRIDEMENT

DESOXYRIBOSE nucleoprotein is a significant constituent of purulent and inflammatory exudates, and may be present in quantities ranging from 30 per cent to 70 per cent of the total purulent sediment. Fibrin also is present in appreciable proportions in purulent material. The discovery that these complexes are important in accounting for such characteristics of pus as thickness, sliminess, viscosity, and stringiness led to considerable in vitro study in search of means of liquefaction. Preparations from hemolytic streptococcal filtrates were shown[1, 2, 3] to contain fibrinolysin, or streptokinase, which liquefies fibrin, and in addition, desoxyribose nuclease, or streptodornase, which brings about liquefaction of both desoxyribose nucleoprotein and desoxyribose nucleic acid. Hemolytic streptococci of group A possess fibrinolytic properties and seem to be uniformly potent in the production of desoxyribose nuclease. Strains of *Streptococcus viridans* and of pneumococci were not found to possess comparable properties. When active streptococcal concentrates are added to whole samples of purulent and inflammatory exudates, rapid lysis of both fibrin and desoxyribose nucleoprotein occurs.

Within the past eighteen months,[4] application of these phenomena has been made therapeutically as an adjunct in the treatment of patients in whom tenacious exudates presented a difficult problem. Empyema pus of bacterial origin is high in nucleoprotein content which is derived presumably from the leucocytes present. In an attempt to bring about rapid lysis of such tenacious exudates, concentrated partially-purified filtrates prepared from broth cultures of hemolytic streptococci were injected into the pleural cavity of selected patients suffering from various conditions which give rise to pleural exudations.

Twenty-three patients were studied following the injection of amounts of streptococcal concentrate sufficient to bring about clear-cut biochemical and biophysical changes in the area of exudation at the site of injection. These changes varied somewhat with the character of the exudate.

Among the twenty-three patients in this treated group were five patients with tuberculous pleurisy with effusion, six patients with primary or metastatic malignancy (pulmonary neoplasm and pleural effusion), and two patients with congestive heart failure with pleural effusion. The activity of the fibrinolytic preparations (streptokinase) was demonstrable in samples of exudate taken at repeated intervals following injection. Intrapleural depolymerization of the nucleoprotein contained in the solid sediment of the exudate was demonstrable in a similar manner (streptodornase). The effects of the concentrates were self-limiting after each injection, varying in duration, however, from several hours to several days. Toxic manifestations following the injection of the concentrates were minimal, being limited to transient febrile reactions with general malaise, and a local outpouring of leucocytes of a few days' duration.

Studies[5] have been made of the possible inhibitory action of various substances on the enzymatic activity of the concentrates containing streptokinase and streptodornase. Salicylate, Gentisate, ascorbate, thiourea, para-aminobenzoic acid, parachlorophenol, oxalate, colchicine, and penicillin showed no inhibitory action. Citrate and heparin were found to exert inhibitory action.

The January, 1950,[6] issue of the *Annals of Surgery* carries a report of the use of streptococcal enzymatic débridement in the treatment of a wider variety of conditions. Concentrates containing streptokinase and streptodornase in sufficient quantity to effect substantial and rapid enzymatic changes can be introduced locally into the thoracic cavity of patients without causing untoward reactions. The authors classify the patients treated into the following categories:

1. Loculated, post-pneumonectomy hemothorax: successful liquefaction of fibrinous exudate allowing removal of fluid within twenty-four hours.
2. Traumatic hemothorax: drainage from a post-traumatic hemothorax was meager with persistence of complete lung collapse. Aspiration of fluid was possible following injection of 100,000 units of streptokinase plus minimal injection of streptodornase. Lung expanded promptly, drainage decreased, recovery was uneventful.
3. Sterile loculated empyema: pleural loculations present; aspiration was possible within twenty-four hours after treatment; thick, greenish, purulent material was liquefied; temperature returned to normal; there was rapid clinical recovery. Streptokinase and streptodornase.
4. Bacterial empyema: pleural effusion was present; thoracentesis yielded thick, greenish, foul-smelling pus from which a strain of anaerobic streptococcus was cultured. Open thoracotomy with drainage tubes. Streptokinase, streptodornase, and penicillin. Aspiration was possible following treatment. Complete recovery. Other cases of this type included one of post-pneumonectomy empyema caused by *Bacillus pyocyaneus*.
5. Treatment of osteomyelitis with chronic draining sinus tract. Culture revealed *Bacillus proteus, B. pyocyaneous,* and *Staphylococcus albus.* Streptokinase and streptodornase. Treatment of maxillary sinusitis: chronic maxillary sinusitis of three years' duration; no spontaneous drainage. Streptokinase and streptodornase assisted in bringing about adequate drainage. Penicillin was used systemically.
6. Chronic ulcerative lesion of leg (etiology unknown). Treated successfully with local application of streptokinase and streptodornase.

In these patients the individual dosage varied from 100,000 to 400,000 units of streptokinase and 5,000 to 40,000 units of streptodornase. The combined units of the two enzymes were contained in 2 to 10 ml. of physiologic salt solution.

Where effective application was accomplished the following changes were observed: a marked thinning of the exudate, an outpouring of viable leucocytes, a decrease in the number of, or disappearance of the locally infecting bacteria, subsequent decrease or disappearance of exudate, and rapid regrowth of tissues and epithelium. Débridement of the site of infection through enzymatic action seems to render the area permeable to the humoral and cellular forces of both

natural and specifically acquired immunity, or to circulating antibiotics, all of which contribute to the elimination of organisms.

Determinations of optimal dosage, frequency of administration, and methods of application must be worked out. The availability of a nontoxic substance with enzymatic activity such as that described in this series of papers will be helpful under a number of circumstances, wherever loculation of fibrin-containing material occurs, or where purulent exudate containing nucleoprotein is present. The use of these enzymes, streptokinase or streptodornase, may offer real possibilities in the treatment of chronic meningeal infections where loculated pus tends to occur at the base of the brain such as in chronic purulent meningitis and particularly in tuberculous meningitis. These substances might prove useful also in the treatment of joints in which purulent exudates are present, or in hemarthrosis such as that which occurs in hemophilia.

RUSSELL J. BLATTNER

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# News and Notes

The following were certified by the **American Board of Pediatrics** at the examination at Philadelphia, Pa., March 31, April 1 and 2, 1950.

Dr. E. Bryce Alpern, Children's Hospital of Michigan, 5224 St. Antoine, Detroit, Mich.
Dr. Rose Grillo Ames, 630 W. 168th St., New York, N. Y.
Dr. Sidney W. Berezin, 54 N. Main St., Spring Valley, N. Y.
Dr. Benjamin B. Berman, 417 Missouri Ave., East St. Louis, Ill.
Dr. John R. Birmingham, Children's Hospital, Detroit, Mich.
Dr. Frederick A. Blount, College Village, Winston-Salem, N. C.
Dr. Stanley L. Blumenthal, 5719 New Hampshire Ave., N.E., Washington, D. C.
Dr. Sylvan A. Broadman, 2901 Glynn Court, Detroit 6, Mich.
Dr. Seymour Charles, 172 Lyons Ave., Newark, N. J.
Dr. Harriet Josephine Davis, 117 E. Oakland Ave., Doylestown, Pa.
Dr. John F. Drumheller, 815 Raspberry St., Erie, Pa.
Dr. Frank Paul Ermilio, 700 Marlyn Rd., Philadelphia 31, Pa.
Dr. Leo Feld, 155 Lexington Ave., Passaic, N. J.
Dr. Jack Russell Frank, 806 Parkerson Ave., Crowley, La.
Dr. George Warren Hallett, Jr., 131 State St., Portland, Me.
Dr. Alvin Beasley Hayles, Mayo Clinic, 102 Second S.W., Rochester, Minn.
Dr. Howard H. Hildebrand, 313 Fifth St., Ames, Iowa.
Dr. Hilbert Paul Jubelt, 111 S. Fourth St., Manhattan, Kan.
Dr. Else Kaufmann, 533 232nd St., New York 63, N. Y.
Dr. Albert Warren Kitts, 202 North Pinehurst Ave., Salisbury, Md.
Dr. Marshall Bradford Kreidberg, 20 Ash St., Boston, Mass.
Dr. Jonathan Trumbull Lanman, Department of Pediatrics, Bellevue Hospital, 28th St., at First Ave., New York, N. Y.
Dr. Ira Wallace Leibner, 470 Ocean Ave., Brooklyn 26, N. Y.
Dr. Irving Levitt, 11368 Kelly Rd., Detroit 24, Mich.
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Dr. Joseph Gibson Lockhart, 5300 Knox St., Philadelphia 44, Pa.
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Dr. William McLean Wallace, 300 Longwood Ave., Boston 15, Mass.
Dr. James I. Wendell, Jr., 758 High St., Pottstown, Pa.
Dr. Seymour E. Wheelock, 1850 Gilpin, Denver, Colo.
Dr. William Eric Williams, 9 Ridge Rd., Rutherford, N. J.

The total number of candidates certified to date by this Board is now 3,254.

Dr. Hugh Leslie Moore of Dallas, Texas, died Jan. 20, 1950, at the age of 75. He was professor of pediatrics at Baylor from 1908 until its removal from Dallas, and subsequently held the same position at Southwestern Medical College. He was active in national and pediatric medical societies and at one time was president of the Southern Medical Association. He was medical director of the Children's Medical Center in Dallas and Chief of Staff at the Bradford Memorial Hospital for Babies.

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Dr. William Boyd Reading of Galveston, Texas, died Feb. 2, 1950, at the age of 60. He was, for many years, professor of pediatrics at the medical school of the University of Texas and chief pediatrician at the John Sealy Hospital.

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A prize of 1,000 dollars, donated by the Kappa Delta Sorority, is awarded annually by the **American Academy of Orthopaedic Surgeons** for the best research done in orthopedic surgery or a related scientific field by an individual in the United States. The second award, for the year 1950, will be presented at the eighteenth annual convention of the Academy in Chicago, Jan. 31, 1951. Researchers interested in competing for this prize are requested to secure further information from Dr. R. Beverly Raney, Duke Hospital, Durham, N. C., Chairman of the Award Committee for 1950.

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Dr. Glidden L. Brooks has resigned as Associate Director of the American Academy of Pediatrics' Committee for the Improvement of Child Health, and has been appointed Co-ordinator of the Medical Center Hospitals and Clinics and Professor of Hospital Administration at the University of Pittsburgh Graduate School of Public Health.

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The department of pediatrics of Washington University School of Medicine, under the direction of Dr. A. F. Hartmann, will again offer a postgraduate course in pediatrics during the fall of 1950. This course will be six weeks in length and will begin Sept. 11, 1950.

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# Book Reviews

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**Clinical ACTH.** Proceedings of the First Clinical ACTH Conference. John R. Mote, M.D., Editor, Philadelphia—Toronto, 1950, The Blakiston Company, 607 pages.

In this book are recorded and discussed fifty-two separate presentations of studies made during the past three years of the effects of ACTH (and sometimes Compound E). Clinical material studied included 53 normal subjects, 73 endocrine abnormalities, 214 collagen diseases, 38 cases of hypersensitivity, 43 infections, 24 malignancies, 70 mental diseases, 16 muscle demyelinating diseases, and 82 miscellaneous diseases. In most of the studies, data were presented in the form of well-drawn charts succinctly described and covering effects on circulating eosinophiles, sodium, potassium, chloride, water, calcium, phosphate and nitrogen balance, blood and urine glucose concentration, and urinary excretion of uric acid and corticoids.

The reader will be impressed by the volume of carefully performed work presented and the excellent editing of its discussion by the many authorities participating in the conference. He will also be intrigued by the occasional attempt to put together the widely varying results and sometimes conflicting opinions in the form of new concepts of endocrine relations to disease, and, above all, will be encouraged by the many striking examples of clinical improvement following ACTH therapy. HARTMANN

**Primer of Allergy.** Warren T. Vaughan, M.D., and J. Harvey Black, M.D., ed. 3, St. Louis, 1950, The C. V. Mosby Company, 175 pages. Price $3.50.

This discussion of allergy for the patient has been very popular, as the first two editions went through several printings. Dr. Black has revised it since Dr. Vaughan's death, bringing it up to date, but maintaining the same form of presentation as the previous editions written by Dr. Vaughan. It is a very useful book for the intelligent patient with an allergic condition, but it is far too technical for general reading.

**Hemolytic Disease of the Newborn.** M. M. Pickles, M.D., Nuffield Graduate Assistant in Clinical Pathology, Radcliffe Infirmary, Oxford. Springfield, Ill., 1949, Charles C Thomas, Publisher, 181 pages, with 21 illustrations and 19 tables. Price $4.50.

A number of recently published books and current articles in the medical literature have dealt with the subject of hemolytic disease of the newborn infant. Some of this material has tended to confuse the physician, especially in the more speculative serologic aspects of the disease. This monograph will be especially welcomed, since the author has written the book with an awareness of this state of affairs and has attempted to set forth the basic facts relating to Rh antigens and antibodies in a simple but authoritative manner. The monograph is well organized and the material is set forth in a succinct and readable style. The text reflects a seasoned and well-informed approach to the study of disease in all its varied clinical and basic serologic aspects. The introductory chapter deals concisely but adequately with the historical evolution of the disease and is an admirable survey of the past and present knowledge of the disorder. The ensuing chapters deal with the Rh antigens and antibodies, their relation to hemolytic disease, and the mechanism of the immunization. This lucid exposition of a difficult subject is particularly commendable and will be especially refreshing to the clinician who has become lost in the vagaries of involved serology. The remaining chapters deal with a combined discussion of the clinical, pathologic, hematologic, and biochemical patterns of the disease and is an excellent integration of basic information and clinical facts. Treatment is critically discussed from practically every aspect with which the practicing physician should be aware. Concluding chapters summarizing some of the practical clinical points of the disease, some of the classical sequelae and suggested manifestations of the disease, set forth valuable prognostic data that should be considered in the total management of the disease. An appendix containing data on serologic techniques, antibody determinations, suggestions for routine ante-natal antibody determination and other valuable technical material, completes the excellent organization of the monograph. This is a book that can be confidently recommended to every practicing pediatrician and general practitioner as a concise, authoritative, and readable source of current information on the subject of hemolytic disease of the newborn infant.

PONCHER.

**Malnutrition and Starvation in Western Netherlands.** September, 1944, to July, 1945. The Hague, 1948, General State Printing Office. Part I. General discussion and reports of various teams. Part II. Thirty-two appendices containing statistical tables.

This is a report on the malnutrition and starvation which developed in western Holland the last year of World War II as a result of the German occupying forces failing to provide sufficient food for the civilian population, and of the work of the groups of public health workers who had been assembled to meet the situation. Advanced stages of starvation were encountered with some individuals having lost over 50 per cent of their normal weight. The relief workers found that predigested foods were not necessary as had been assumed in preparing for the situation, and that there was little evidence of the avitaminoses. Hunger edema was common but could not be explained on the basis of lowered plasma protein and osmosis. The most striking finding was the rapidity with which the starved individuals could digest and assimilate large quantities of food.

# Editor's Column

## RETROLENTAL FIBROPLASIA

OPHTHALMOLOGISTS through the years have occasionally noted the condition often called retinal folds which consists usually in a tubelike gray elevation, extending from the optic nerve head temporally and upward, markedly elevated, and spreading funnel-shaped toward the equator of the lens. This was presumed to be a congenital defect.

In 1942, Dr. T. L. Terry described this condition, or one similar to it in some of its aspects, as occurring in premature infants. He named this disease "retrolental fibroplasia." He wrote several papers on it in 1942 and 1943, describing it as a fibroblastic overgrowth of persistent tunica vasculosa lentis in premature infants. After he had called attention to it, many ophthalmologists began to observe similar conditions in children whose birth weight was less than 2,000 grams. There was great variability in different cases, the outstanding features being the prematurity and new tissue formation in the retina or vitreous and especially on the posterior surface of the lens. Since this time, controversy has raged as to the nature of the process, its etiology, and its treatment. The literature in the past eight years has become voluminous. Terry himself unfortunately died shortly after he reported this condition. Important students of the disease have been Drs. A. B. Reese, William C. Owens working with Ella U. Owens, his wife, and Dr. A. C. Krause. In the most recent paper of Owens and Owens there are no less than thirty-three references.

One might divide the controversy of etiology and development into two schools of thought; one that is championed primarily by Reese and others who hold that the condition is congenital and can be divided into two groups; one, which is relatively rare, consists in persistence and hyperplasia of the primary vitreous, and two, retrolental fibroplasia. The second school of thought championed by Owens and Owens and others contends that the condition is not present at birth, but develops after the first few months of life in the premature infant. The importance of the condition may be gathered from the estimate of Reese that a third of all cases of blindness in preschool children now are due to retrolental fibroplasia and that "there are indications that the incidence has increased not only in the past decade or more, but even more during the past few years."

Reese describes the histologic picture of the condition that he contends is persistence and hyperplasia of the primary vitreous as characterized by dense fibrous tissue along the posterior surface of the lens, thickest in the central portion and thinning toward the periphery. He states further that the hyaloid artery is usually persistent and extends to the optic disc. The ciliary processes are elongated and reach into the periphery of the fibrous tissue. The retina, however, appears to have all its elements and to be capable of functioning. Occasionally the lens is swollen due to a dehiscence in the posterior capsule causing the lens to press against the cornea. This disease occurs generally in full-term

infants who develop normally, and it affects only one eye. The condition is usually seen at, or shortly after, birth.

Retrolental fibroplasia, on the other hand, is thought by Reese to be due to the persistence of some of the vascular primary vitreous in the region of the base of the vitreous. This tissue does not seem to be in the retina, but definitely internal to the retina. Reese thinks that "an important embryologic feature of this condition is the adherence of this persistent vitreous to the adjacent inner layer of the optic cup. Over this layer the secondary vitreous fails to form, and therefore the retina is detached. The subsequent hemorrhage organization and contraction lead to further retinal detachment." The clinical appearance is of a gray, seemingly opaque, or opaque tissue in the anterior part of the vitreous immediately behind the lens. Occasionally blood vessels are seen in it, as are also hemorrhages. Reese contends that the child should be examined under anesthesia, the eye rotated with forceps, and pressure made in the region of the ora serrata in order to make a satisfactory examination. Shallowness of the anterior chamber is always to be found and glaucoma is not rare. Both eyes are affected. According to Reese, it can occur in full-term infants and he states that the condition occurs in one or more of twins and triplets in from 10 to 15 per cent of cases. An interesting pathologic condition associated with retrolental fibroplasia in about a quarter of the cases is elevated skin hemangiomas, often multiple and widespread, present at birth. Another feature is vaginal bleeding of the mothers during pregnancy in approximately 30 to 35 per cent of the cases. Dr. Reese thinks that, since he believes all cases to be congenital, one must look to the mother as the medium. The incidence varies with the locality, apparently being rare in some parts of America and common in others; again quoting Reese and his colleagues rare "in France, Austria, and Australia." He believes that fibroplasia is ten times as frequent as hyperplasia of the vitreous. Since Dr. Reese thinks that in cases of hyperplasis of the vitreous the retina is normal, it may be possible to remove or destroy the thickened membrane behind the lens. He suggests an operation and reports five cases. In none was the condition made worse and possibly there was some improvement in one or two.

Owens and Owens review the subject in the *American Journal of Ophthalmology* for January, 1949, and add much of importance to the literature of the subject. They reviewed hospital records of premature infants weighing 2,000 grams or less in the ten-year period from 1935 to 1944. One hundred twenty children, ranging from one to 8 years of age, returned to the hospital for examination at their request. None had retrolental fibroplasia. In the current group, from July, 1945, to June, 1947, 214 premature infants weighing up to 2,000 grams were examined and none showed retrolental fibroplasia at birth. Of 111, followed for six months or more, five developed retrolental fibroplasia, four of these being in the group of those who weighed less than 1,360 grams at birth, and one in the group that weighed 1,360 to 2,000 grams. Of the 214 premature infants who did not show retrolental fibroplasia at birth, they saw retrolental fibroplasia develop in nine cases.

A condensation of their description of the development of the lesion follows: Remains of the hyaloid system disappeared early in postnatal life; early observations of the external appearance of the eyes and fundi were normal. Dilatation and tortuosity of both the arteries and the veins, especially the latter, gradually increased. Next one or more small grayish-yellow elevations of the retina appeared in the far periphery. Soon the margins of the disc became blurred and generalized retinal edema developed. Other grayish-yellow areas appeared scattered throughout the fundus. After a short time, a gray membrane, resembling swollen retina, with numerous vessels coursing over it billowed forward in folds at the periphery of the retrolental space. At this stage the fundus could be only hazily seen. Bands of tissue extended from the areas of detached retina into the vitreous.

Finally a complete retrolental membrane was formed by gradual extension and fusion of the peripheral folds of the retina. Broad ciliary processes were seen extending onto the membrane at its periphery and numerous vessels were present on the surface of the membrane. Occasionally small hemorrhages occurred into the membrane from these vessels. The anterior chamber became shallow. Posterior synechias formed and the iris developed a grayish atrophic appearance.

Later some of the eyes showed secondary changes. These consisted of further shallowing of the anterior chamber with extension forward of the iris and lens in a domelike fashion. The tension rose, the cornea became cloudy and the eyes enlarged. In some cases this phase was transient, the anterior chamber later became deeper with clearing of the cornea and return of the tension to normal.

"In all cases the disease did not progress to the formation of complete retrolental membranes in both eyes. Occasionally the course of the disease was arrested at some stage in its progress, producing an incomplete picture."

Reese contends that since the disease starts, in his opinion, far anteriorly, unless the greatest care in examination after the method he has described is used, the early changes may be overlooked. Furthermore, he believes that there is an area in the anterior vitreous which can under no circumstances be seen, so that on clinical examination alone one may overlook the primary lesion if extremely anterior.

The Owenses thought that since the disease develops postnatally, treatment to the child might be of value. They were struck by the possibility that there might be a deficiency of vitamin E in premature infants developing retrolental fibroplasia. Since a low fat diet has been recommended for premature infants, probably there is a shortage of fat-soluble vitamins. Vitamins A, D, and K have usually been supplied, but not vitamin E. Experimentally it has been shown that when additional vitamin A or unsaturated fats have been given to animals, additional vitamin E is required. This might seem to indicate an even greater vitamin E deficiency in the premature infant given such a diet.

They determined the average level of vitamin E in babies not receiving vitamin E supplements and found them to average 0.25 mg. per cent. It was

possible to raise this level to 4.12 mg. per cent by giving 115 mg. dl alpha-tocopheryl acetate daily. However, they say that there seemed to be no constant correlation between the serum tocopherol level and the occurrence of retrolental fibroplasia. Their figures are impressive:

A total of 101 premature infants with birth weights of 1,360 grams (3 pounds) or less have been observed at routine intervals since birth. Twenty-three of these infants received supplements of dl alphatocopheryl acetate. One of these (4.4 per cent) developed retrolental fibroplasia. Seventy-eight infants did not receive supplements of dl alphatocopheryl acetate. Seventeen of these (21.8 per cent) developed retrolental fibroplasia.

The Owens' work would seem to suggest a satisfactory treatment and perhaps a solution of the whole problem.

Undoubtedly the incidence of these fibroblastic conditions in infants has enormously increased in the past few years. In my own experience I have seen about five times as many cases in the last five years as I saw in the preceding thirty. Several factors may be responsible for this; primarily, the life of the premature child is being saved far more frequently than heretofore; also, the attention of ophthalmologists has been drawn to the condition since 1942, and more cases are correctly classified that were previously thought to be retinoblastomas or other diseases. It seems that the increase is greater than these factors alone would indicate. It may be, therefore, that some foods, drugs, or treatment that are given to the premature child may be a factor.

If one believes with Reese that all cases of this disease are congenital in origin, the cause must be sought in the mother. If, however, the Owenses are correct in contending that the disease develops after birth, one would look for something in the treatment of the child. Studies have not revealed any particularly suggestive factors in the mothers of these children. The only idea for treatment is that of the Owenses. Their work indicates that this must be begun before the disease becomes evident. Most cases, when they are seen, are too advanced for vitamin E therapy to be valuable. On the evidence presented by the Owenses, and thus far not refuted, it would seem wise to begin supplementary vitamin E therapy in the amount necessary in all premature children, especially if of low birth weight, and furthermore since the disease occurs occasionally in apparently normal children born at full term, it might be wise to be sure that that body content of vitamin E was adequate in all babies, especially if low fat or high vitamin A diets are to be ordered. However, this work is only in a preliminary stage and quite possibly other factors than vitamin E deficiency may be responsible for the condition. This is especially probable, since several patients who have had adequate vitamin E have nevertheless developed the disease.

LAWRENCE T. POST, M.D.

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1. Jeans, P. C., and Marriott, W. M.: Infant Nutrition, C. V. Mosby Co., 4th ed., p. 140.
2. Hilditch, T. P.: The Chemical Composition of Natural Fats, John Wiley & Sons, 2nd ed. rev., p. 127.
3. Brennemann, J.: Practice of Pediatrics, W. F. Prior Co., vol. I, chap. 26, p. 3.


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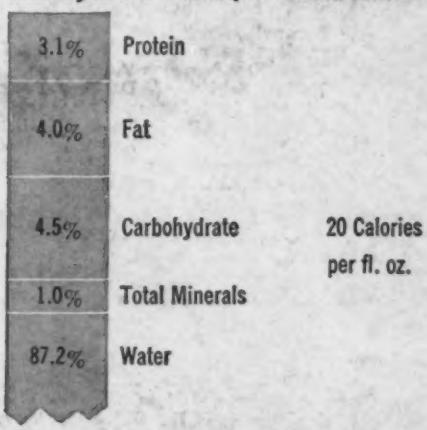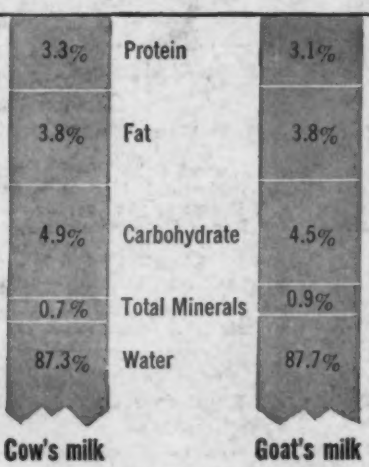
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